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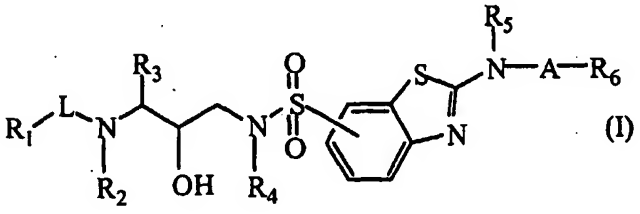
(54) Title: BROADSPECTRUM 2-(SUBSTITUTED-AMINO)-BENZOTHIAZOLE SULFONAMIDE HIV PROTEASE INHIBITORS



(I)

(57) Abstract: The present invention concerns the compounds having the formula (I), N-oxides, salts, stereoisomeric forms, racemic mixtures, prodrugs, esters and metabolites thereof, wherein R_1 and R_8 each are H, optionally substituted C_{1-6}alkyl, C_2-6alkenyl, C_{3-7}cycloalkyl, aryl, Het^1, Het^2; R_1 may also be a radical of formula $(R_{11a}R_{11b})NC(R_{10a}R_{10b})CR_{9-}$; t is 0, 1 or 2; R_2 is H or C_{1-6}alkyl; L is -C(=O)-, -O-C(=O)-, $-NR_8$-C(=O)-, -O-C_{1-6}alkanediyl-C(=O)-, $-NR_8$-C_1-6?alkanediyl-C(=O)-, -S(=O)2-, -O-$S(=O)_{2-}$, -NR8-$S(=O)_2$; R3 is C_{1-6}alkyl, aryl, C_{3-7}cycloalkyl, C_{3-7}cycloalkylC_{1-4}alkyl, or arylC_{1-4}alkyl; R_4 is H, C_{1-4}alkylOC(=O), carboxyl, aminoC(=O), mono- or di(C_{1-4}alkyl)aminoC(=O), C_{3-7}cycloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl or optionally substituted C_{1-6}alkyl; A is C_{1-6}alkanediyl, -C(=O)-, -C(=S)-, -$S(=O)_{2-}$, C_{1-6}alkanediyl-C(=O)-, C_{1-6}alkanediyl-C(=S)- or C_{1-6}alkanediyl-$S(=O)_{2-}$; R_5 is H, OH, C_{1-6}alkyl, Het^1C_{1-6}alkyl, Het^2C_{1-6}alkyl, optionally substituted aminoC_{1-6}alkyl; R_6 is C_{1-6}alkylO, Het^1, Het^1O, Het^2, Het^2O, aryl, arylO, C_{1-6}alkyloxycarbonylamino or amino; and in case -A- is other than C_{1-6}alkanediyl then R^6 may also be C_{1-6}alkyl, Het^1C_{1-4}alkyl, Het^1OC_{1-4}alkyl, Het^2C_{1-4}alkyl, Het^2OC_{1-4}alkyl, arylC_{1-4}alkyl, arylOC_{1-4}alkyl or aminoC_{1-4}alkyl; whereby each of the amino groups in the definition of R^6 may optionally be substituted; R^5 and -A-R^6 taken together with the nitrogen atom to which they are attached may also form Het^1 or Het^2. It further relates to their use as broadspectrum HIV protease inhibitors, processes for their preparation as well as pharmaceutical compositions and diagnostic kits comprising them. It also concerns combinations thereof with another anti-retroviral agent, and to their use in assays as reference compounds or as reagents.

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BROADSPECTRUM 2-(SUBSTITUTED-AMINO)-BENZOTHIAZOLE SULFONAMIDE HIV PROTEASE INHIBITORS

The present invention relates to 2-(substituted-amino)-benzothiazole sulfonamides, their use as aspartic protease inhibitors, in particular as broadspectrum HIV protease inhibitors, processes for their preparation as well as pharmaceutical compositions and diagnostic kits comprising them. The present invention also concerns combinations of the present 2-(substituted-amino)-benzothiazole sulfonamides with another anti-retroviral agent. It further relates to their use in assays as reference compounds or as reagents.

The virus causing the acquired immunodeficiency syndrome (AIDS) is known by different names, including T-lymphocyte virus III (HTLV-III) or lymphadenopathy-associated virus (LAV) or AIDS-related virus (ARV) or human immunodeficiency virus (HIV). Up until now, two distinct families have been identified, i.e. HIV-1 and HIV-2. Hereinafter, HIV will be used to generically denote these viruses.

One of the critical pathways in a retroviral life cycle is the processing of polyprotein precursors by aspartic protease. For instance with the HIV virus the *gag-pol* protein is processed by HIV protease. The correct processing of the precursor polyproteins by the aspartic protease is required for the assembly of infectious virions, thus making the aspartic protease an attractive target for antiviral therapy. In particular for HIV treatment, the HIV protease is an attractive target.

HIV protease inhibitors (PIs) are commonly administered to AIDS patients in combination with other anti-HIV compounds such as, for instance nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs) or other protease inhibitors. Despite the fact that these antiretrovirals are very useful, they have a common limitation, namely, the targeted enzymes in the HIV virus are able to mutate in such a way that the known drugs become less effective, or even ineffective against these mutant HIV viruses. Or, in other words, the HIV virus creates an ever increasing resistance against the available drugs.

Resistance of retroviruses, and in particular the HIV virus, against inhibitors is a major cause of therapy failure. For instance, half of the patients receiving anti-HIV combination therapy do not respond fully to the treatment, mainly because of resistance of the virus to one or more drugs used. Moreover, it has been shown that resistant virus is carried over to newly infected individuals, resulting in severely limited therapy options for these drug-naive patients. Therefore, there is a need in the art for new

compounds for retrovirus therapy, more particularly for AIDS therapy. The need in the art is particularly acute for compounds that are active not only on wild type HIV virus, but also on the increasingly more common resistant HIV viruses.

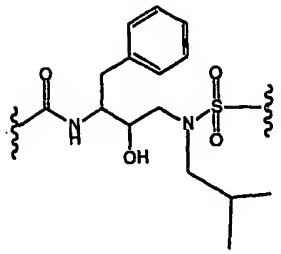
Known antiretrovirals, often administered in a combination therapy regimen, will eventually cause resistance as stated above. This often may force the physician to boost the plasma levels of the active drugs in order for said antiretrovirals to regain effectivity against the mutated HIV viruses. The consequence of which is a highly undesirable increase in pill burden. Boosting plasma levels may also lead to an increased risk of non-compliance with the prescribed therapy. Thus, it is not only important to have compounds showing activity for a wide range of HIV mutants, it is also important that there is little or no variance in the ratio between activity against mutant HIV virus and activity against wild type HIV virus (also defined as fold resistance or FR) over a broad range of mutant HIV strains. As such, a patient may remain on the same combination therapy regimen for a longer period of time since the chance that a mutant HIV virus will be sensitive to the active ingredients will be increased.

Finding compounds with a high potency on the wild type and on a wide variety of mutants is also of importance since the pill burden can be reduced if therapeutic levels are kept to a minimum. One way of reducing this pill burden is finding anti-HIV compounds with good bioavailability, i.e. a favorable pharmacokinetic and metabolic profile, such that the daily dose can be minimized and consequently also the number of pills to be taken.

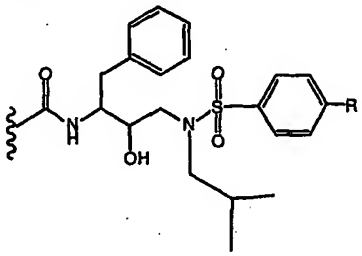
Another important characteristic of a good anti-HIV compound is that plasma protein binding of the inhibitor has minimal or even no effect on its potency.

Thus, there is a high medical need for protease inhibitors that are able to combat a broad spectrum of mutants of the HIV virus with little variance in fold resistance, have a good bioavailability and experience little or no effect on their potency due to plasma protein binding.

Up until now, several protease inhibitors are on the market or are being developed. One particular core structure (depicted below) has been disclosed in a number of references, such as, WO 95/06030, WO 96/22287, WO 96/28418, WO 96/28463, WO 96/28464, WO 96/28465 and WO 97/18205. The compounds disclosed therein are described as retroviral protease inhibitors.



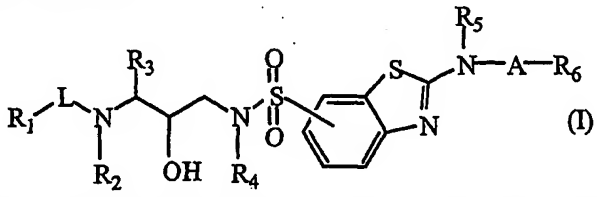
WO 99/67254 discloses 4-substituted-phenyl sulfonamides capable of inhibiting multi-drug resistant retroviral proteases.



Surprisingly, the 2-(substituted-amino)-benzothiazole sulfonamides of the present invention are found to have a favorable pharmacological and pharmacokinetic profile. Not only are they active against wild-type HIV virus, but they also show a broadspectrum activity against various mutant HIV viruses exhibiting resistance against known protease inhibitors.

Though some of the present 2-(substituted-amino)-benzothiazole sulfonamides appear to fall within the generic description of some of the above cited patent publications, they are not specifically disclosed, suggested or claimed therein, nor would a person skilled in the art have been motivated to design them as broadspectrum protease inhibitors.

The present invention concerns 2-(substituted-amino)-benzothiazole protease inhibitors, having the formula

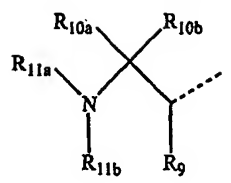


(I)

and *N*-oxides, salts, stereoisomeric forms, racemic mixtures, prodrugs, esters and metabolites thereof, wherein

R_1 and R_8 are, each independently, hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, arylC_{1-6}alkyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkylC_{1-6}alkyl, aryl, Het^1, Het^1C_{1-6}alkyl, Het^2 or Het^2C_{1-6}alkyl;

R_1 may also be a radical of formula



(II)

wherein

R_9 , R_{10a} and R_{10b} are, each independently, hydrogen, C_{1-4}alkyloxycarbonyl, carboxyl, , aminocarbonyl, mono- or di(C_{1-4}alkyl)aminocarbonyl, C_{3-7}cycloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl or C_{1-4}alkyl optionally substituted with aryl, Het^1, Het^2, C_{3-7}cycloalkyl, C_{1-4}alkyloxycarbonyl, carboxyl, aminocarbonyl, mono- or di(C_{1-4}alkyl)aminocarbonyl, aminosulfonyl, C_{1-4}alkyl$S(O)_t$, hydroxy, cyano, halogen or amino optionally mono- or disubstituted where the substituents are selected from C_{1-4}alkyl, aryl, arylC_{1-4}alkyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkylC_{1-4}alkyl, Het^1, Het^2, Het^1C_{1-4}alkyl and Het^2C_{1-4}alkyl; whereby R_9, R_{10a} and the carbon atoms to which they are attached may also form a C_{3-7}cycloalkyl radical; when L is -O-C_{1-6}alkanediyl-C(=O)- or -NR_8-C_{1-6}alkanediyl-C(=O)-, then R9 may also be oxo;

R_{11a} is hydrogen, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-7}cycloalkyl, aryl, arylC_{1-4}alkyl, aminocarbonyl optionally mono- or disubstituted, aminoC_{1-4}alkyl-carbonyloxy optionally mono- or disubstituted, C_{1-4}alkyloxycarbonyl, aryloxycarbonyl, Het^1oxycarbonyl, Het^2oxycarbonyl, aryloxycarbonylC_{1-4}alkyl, arylC_{1-4}alkyloxycarbonyl, C_{1-4}alkylcarbonyl, C_{3-7}cycloalkyl-carbonyl, C_{3-7}cycloalkylC_{1-4}alkyloxycarbonyl, C_{3-7}cycloalkylcarbonyloxy, carboxylC_{1-4}alkylcarbonyloxy, C_{1-4}alkylcarbonyloxy, arylC_{1-4}alkyl-carbonyloxy, arylcarbonyloxy, aryloxycarbonyloxy, Het^1carbonyl, Het^1carbonyloxy, Het^1C_{1-4}alkyloxycarbonyl, Het^2carbonyloxy, Het^2C_{14}alkylcarbonyloxy, Het^2C_{1-4}alkyloxycarbonyloxy or C_{1-4}alkyl optionally substituted with aryl, aryloxy, Het^2 , halogen or hydroxy; wherein the substituents on the amino groups are each independently selected from C_{1-4}alkyl, aryl, arylC_{1-4}alkyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkylC_{1-4}alkyl, Het^1, Het^2, Het^1C_{1-4}alkyl and Het^2C_{1-4}alkyl;

R_{11b} is hydrogen, C_{3-7}cycloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, aryl, C_{1-6}alkyl-oxycarbonyl, Het^1, Het^2 or C_{1-4}alkyl optionally substituted with halogen, hydroxy, C_{1-4}alkyl$S(=O)_t$, aryl, C_{3-7}cycloalkyl, Het^1, Het^2, amino optionally mono- or disubstituted where the substituents are selected from C_{1-4}alkyl, aryl, arylC_{1-4}alkyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkylC_{1-4}alkyl, Het^1, Het^2, Het^1C_{1-4}alkyl and Het^2C_{1-4}alkyl;

whereby R_{11b} may be linked to the remainder of the molecule via a sulfonyl group;

each independently t is zero, 1 or 2;

R_2 is hydrogen or C_{1-6}alkyl;

L is -C(=O)-, -O-C(=O)-, -NR_8-C(=O)-, -O-C_{1-6}alkanediyl-C(=O)-, -NR_8-C_{1-6}-alkanediyl-C(=O)-, -S(=O)$_2$-, -O-S(=O)$_2$-, -NR_8-S(=O)$_2$ whereby either the C(=O) group or the S(=O)$_2$ group is attached to the NR_2 moiety; and whereby the alkanediyl moiety is optionally substituted with aryl, arylC_{1-4}alkyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkylC_{1-4}alkyl, Het^1, Het^2, Het^1C_{1-4}alkyl and Het^2C_{1-4}alkyl;

R_3 is C_{1-6}alkyl, aryl, C_{3-7}cycloalkyl, C_{3-7}cycloalkylC_{1-4}alkyl, or arylC_{1-4}alkyl;

R_4 is hydrogen, C_{1-4}alkyloxycarbonyl, carboxyl, aminocarbonyl, mono- or di(C_{1-4}alkyl)aminocarbonyl, C_{3-7}cycloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl or C_{1-6}alkyl optionally substituted with aryl, Het^1, Het^2, C_{3-7}cycloalkyl, C_{1-4}alkyloxycarbonyl, carboxyl, aminocarbonyl, mono- or di(C_{1-4}alkyl)aminocarbonyl, aminosulfonyl, C_{1-4}alkylS(=O)$_t$, hydroxy, cyano, halogen or amino optionally mono- or disubstituted where the substituents are selected from C_{1-4}alkyl, aryl-C_{1-4}alkyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkylC_{1-4}alkyl, Het^1, Het^2, Het^1C_{1-4}alkyl and Het^2C_{1-4}alkyl;

A is C_{1-6}alkanediyl, -C(=O)-, -C(=S)-, -S(=O)$_2$-, C_{1-6}alkanediyl-C(=O)-, C_{1-6}alkanediyl-C(=S)- or C_{1-6}alkanediyl-S(=O)$_2$-; whereby the point of attachment to the nitrogen atom is the C_{1-6}alkanediyl group in those moieties containing said group;

R_5 is hydrogen, hydroxy, C_{1-6}alkyl, Het^1C_{1-6}alkyl, Het^2C_{1-6}alkyl, aminoC_{1-6}alkyl whereby the amino group may optionally be mono- or di-substituted with C_{1-4}alkyl;

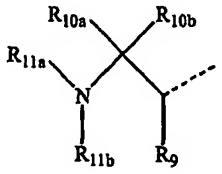
R_6 is C_{1-6}alkyloxy, Het^1, Het^1oxy, Het^2, Het^2oxy, aryl, aryloxy or amino; and in case -A- is other than C_{1-6}alkanediyl then R^6 may also be C_{1-6}alkyl, Het^1C_{1-4}alkyl, Het^1oxyC_{1-4}alkyl, Het^2C_{1-4}alkyl, Het^2oxyC_{1-4}alkyl, arylC_{1-4}alkyl, aryloxyC_{1-4}alkyl or aminoC_{1-4}alkyl; whereby each of the amino groups in the definition of R_6 may optionally be substituted with one or more substituents selected from C_{1-4}alkyl, C_{1-4}alkylcarbonyl, C_{1-4}alkyloxycarbonyl, aryl, arylcarbonyl, aryloxycarbonyl, Het^1, Het^2, arylC_{1-4}alkyl, Het^1C_{1-4}alkyl or Het^2C_{1-4}alkyl; and

R^5 and –A-R^6 taken together with the nitrogen atom to which they are attached may also form Het^1 or Het^2.

According to one embodiment, the present invention concerns 2-(substituted-amino)-benzothiazole protease inhibitors of formula (I), and *N*-oxides, salts, stereoisomeric forms, racemic mixtures, prodrugs, esters and metabolites thereof, wherein

R_1 and R_8 are, each independently, hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, arylC_{1-6}alkyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkylC_{1-6}alkyl, aryl, Het^1, Het^1C_{1-6}alkyl, Het^2, Het^2C_{1-6}alkyl;

R_1 may also be a radical of formula



(II)

wherein

R_9 , R_{10a} and R_{10b} are, each independently, hydrogen, C_{1-4}alkyloxycarbonyl, carboxyl, aminocarbonyl, mono- or di(C_{1-4}alkyl)aminocarbonyl, C_{3-7}cycloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl or C_{1-4}alkyl optionally substituted with aryl, Het^1, Het^2, C_{3-7}cycloalkyl, C_{1-4}alkyloxycarbonyl, carboxyl, aminocarbonyl, mono- or di(C_{1-4}alkyl)aminocarbonyl, aminosulfonyl, C_{1-4}alkyl$S(O)_t$, hydroxy, cyano, halogen or amino optionally mono- or disubstituted where the substituents are selected from C_{1-4}alkyl, aryl, arylC_{1-4}alkyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkylC_{1-4}alkyl, Het^1, Het^2, Het^1C_{1-4}alkyl and Het^2C_{1-4}alkyl; whereby R_9, R_{10a} and the carbon atoms to which they are attached may also form a C_{3-7}cycloalkyl radical;

R_{11a} is hydrogen, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-7}cycloalkyl, aryl, aminocarbonyl optionally mono- or disubstituted, aminoC_{1-4}alkylcarbonyloxy optionally mono- or disubstituted, C_{1-4}alkyloxycarbonyl, aryloxycarbonyl, Het^1oxycarbonyl, Het^2oxycarbonyl, aryloxycarbonylC_{1-4}alkyl, arylC_{1-4}alkyloxycarbonyl, C_{1-4}alkylcarbonyl, C_{3-7}cycloalkylcarbonyl, C_{3-7}cycloalkylC_{1-4}alkyloxycarbonyl, C_{3-7}cycloalkylcarbonyloxy, carboxylC_{1-4}alkylcarbonyloxy, C_{1-4}alkylcarbonyloxy, arylC_{1-4}alkylcarbonyloxy, arylcarbonyloxy, aryloxycarbonyloxy, Het^1carbonyl, Het^1carbonyloxy, Het^1C_{1-4}alkyloxycarbonyl, Het^2carbonyloxy, Het^2C_{1-4}alkylcarbonyloxy, Het^2C_{1-4}alkyloxycarbonyloxy or C_{1-4}alkyl optionally substituted with aryl, aryloxy, Het^2 or hydroxy; wherein the substituents on the amino groups are each independently selected from C_{1-4}alkyl, aryl, arylC_{1-4}alkyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkylC_{1-4}alkyl, Het^1, Het^2, Het^1C_{1-4}alkyl and Het^2C_{1-4}alkyl;

R_{11b} is hydrogen, C_{3-7}cycloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, aryl, Het^1, Het^2 or C_{1-4}alkyl optionally substituted with halogen, hydroxy, C_{1-4}alkyl$S(=O)_t$, aryl, C_{3-7}cycloalkyl, Het^1, Het^2, amino optionally mono- or disubstituted where the substituents are selected from C_{1-4}alkyl, aryl, arylC_{1-4}alkyl,

C_{3-7}cycloalkyl, C_{3-7}cycloalkylC_{1-4}alkyl, Het^1, Het^2, Het^1C_{1-4}alkyl and Het^2C_{1-4}alkyl;

whereby R_{11b} may be linked to the remainder of the molecule via a sulfonyl group;

each independently t is zero, 1 or 2;

R_2 is hydrogen or C_{1-6}alkyl;

L is -C(=O)-, -O-C(=O)-, -NR_8-C(=O)-, -O-C_{1-6}alkanediyl-C(=O)-, -NR_8-C_{1-6}alkanediyl-C(=O)-, -S(=O)$_2$-, -O-S(=O)$_2$-, -NR_8-S(=O)$_2$ whereby either the C(=O) group or the S(=O)$_2$ group is attached to the NR_2 moiety;

R_3 is C_{1-6}alkyl, aryl, C_{3-7}cycloalkyl, C_{3-7}cycloalkylC_{1-4}alkyl, or arylC_{1-4}alkyl;

R_4 is hydrogen, C_{1-4}alkyloxycarbonyl, carboxyl, aminocarbonyl, mono- or di(C_{1-4}alkyl)aminocarbonyl, C_{3-7}cycloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl or C_{1-6}alkyl optionally substituted with aryl, Het^1, Het^2, C_{3-7}cycloalkyl, C_{1-4}alkyloxycarbonyl, carboxyl, aminocarbonyl, mono- or di(C_{1-4}alkyl)aminocarbonyl, aminosulfonyl, C_{1-4}alkylS(=O)$_t$, hydroxy, cyano, halogen or amino optionally mono- or disubstituted where the substituents are selected from C_{1-4}alkyl, aryl, aryl-C_{1-4}alkyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkylC_{1-4}alkyl, Het^1, Het^2, Het^1C_{1-4}alkyl and Het^2C_{1-4}alkyl;

A is C_{1-6}alkanediyl, -C(=O)-, -C(=S)-, -S(=O)$_2$-, C_{1-6}alkanediyl-C(=O)-, C_{1-6}alkanediyl-C(=S)- or C_{1-6}alkanediyl-S(=O)$_2$-; whereby the point of attachment to the nitrogen atom is the C_{1-6}alkanediyl group in those moieties containing said group;

R_5 is hydrogen, hydroxy, C_{1-6}alkyl, Het^1C_{1-6}alkyl, Het^2C_{1-6}alkyl, aminoC_{1-6}alkyl whereby the amino group may optionally be mono- or di-substituted with C_{1-4}alkyl;

R_6 is C_{1-6}alkyloxy, Het^1, Het^1oxy, Het^2, Het^2oxy, aryl, aryloxy or amino; and in case -A- is other than C_{1-6}alkanediyl then R^6 may also be C_{1-6}alkyl, Het^1C_{1-4}alkyl, Het^1oxyC_{1-4}alkyl, Het^2C_{1-4}alkyl, Het^2oxyC_{1-4}alkyl, arylC_{1-4}alkyl, aryloxyC_{1-4}alkyl or aminoC_{1-4}alkyl; whereby each of the amino groups in the definition of R_6 may optionally be substituted with one or more substituents selected from C_{1-4}alkyl, C_{1-4}alkylcarbonyl, C_{1-4}alkyloxycarbonyl, aryl, arylcarbonyl, aryloxycarbonyl, Het^1, Het^2, arylC_{1-4}alkyl, Het^1C_{1-4}alkyl or Het^2C_{1-4}alkyl; and

R^5 and --A-R^6 taken together with the nitrogen atom to which they are attached may also form Het^1 or Het^2.

This invention also envisions the quaternization of the nitrogen atoms of the present compounds. A basic nitrogen can be quaternized with any agent known to those of ordinary skill in the art including, for instance, lower alkyl halides, dialkyl sulfates, long chain halides and aralkyl halides.

Whenever the term "substituted" is used in defining the compounds of formula (I), it is meant to indicate that one or more hydrogens on the atom indicated in the expression using "substituted" is replaced with a selection from the indicated group, provided that the indicated atom's normal valency is not exceeded, and that the substitution results in a chemically stable compound, i.e. a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into a therapeutic agent.

As used herein, the term "halo" or "halogen" as a group or part of a group is generic for fluoro, chloro, bromo or iodo.

The term "C_{1-4}alkyl" as a group or part of a group defines straight and branched chained saturated hydrocarbon radicals having from 1 to 4 carbon atoms, such as, for example, methyl, ethyl, propyl, butyl and 2-methyl-propyl, the like.

The term "C_{1-6}alkyl" as a group or part of a group defines straight and branched chained saturated hydrocarbon radicals having from 1 to 6 carbon atoms such as the groups defined for C_{1-4}alkyl and pentyl, hexyl, 2-methylbutyl, 3-methylpentyl and the like.

The term "C_{1-6}alkanediyl" as a group or part of a group defines bivalent straight and branched chained saturated hydrocarbon radicals having from 1 to 6 carbon atoms such as, for example, methylene, ethan-1,2-diyl, propan-1,3-diyl, propan-1,2-diyl, butan-1,4-diyl, pentan-1,5-diyl, hexan-1,6-diyl, 2-methylbutan-1,4-diyl, 3-methylpentan-1,5-diyl and the like.

The term "C_{2-6}alkenyl" as a group or part of a group defines straight and branched chained hydrocarbon radicals having from 2 to 6 carbon atoms containing at least one double bond such as, for example, ethenyl, propenyl, butenyl, pentenyl, hexenyl and the like.

The term "C_{2-6}alkynyl" as a group or part of a group defines straight and branched chained hydrocarbon radicals having from 2 to 6 carbon atoms containing at least one triple bond such as, for example, ethynyl, propynyl, butynyl, pentynyl, hexynyl and the like.

The term "C_{3-7}cycloalkyl" as a group or part of a group is generic to cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl.

The term "aryl" as a group or part of a group is meant to include phenyl and naphtyl which both may be optionally substituted with one or more substituents independently selected from C_{1-6}alkyl, C_{1-6}alkyloxy, halogen, hydroxy, optionally mono- or disubstituted amino, nitro, cyano, haloC_{1-6}alkyl, carboxyl, C_{1-6}alkoxycarbonyl, C_{3-7}cycloalkyl, Het[1], optionally mono- or disubstituted aminocarbonyl, optionally

mono- or disubstituted aminoC_{1-6}alkyl, methylthio, methylsulfonyl, and phenyl optionally substituted with one or more substituents selected from C_{1-6}alkyl, C_{1-6}alkyloxy, halogen, hydroxy, optionally mono- or disubstituted amino, nitro, cyano, haloC_{1-6}alkyl, carboxyl, C_{1-6}alkoxycarbonyl, C_{3-7}cycloalkyl, Het^1, optionally mono- or disubstituted aminocarbonyl, methylthio and methylsulfonyl; whereby the optional substituents on any amino function are independently selected from C_{1-6}alkyl, C_{1-6}alkylcarbonyl, C_{1-6}alkyloxy-A-, Het^1-A-, Het^1C_{1-6}alkyl, Het^1C_{1-6}alkyl-A-, Het^1oxy-A-, Het^1oxyC_{1-4}akyl-A-, phenyl-A-, phenyl-oxy-A-, phenyloxyC_{1-4}alkyl-A-, phenylC_{1-6}alkyl-A-, C_{1-6}alkyloxycarbonylamino-A-, amino-A-, aminoC_{1-6}alkyl and aminoC_{1-6}alkyl-A- whereby each of the amino groups may optionally be mono- or where possible di-substituted with C_{1-4}alkyl and whereby A is as defined above.

The term "haloC_{1-6}alkyl" as a group or part of a group is defined as C_{1-6}alkyl substituted with one or more halogen atoms, preferably, chloro or fluoro atoms, more preferably fluoro atoms. Preferred haloC_{1-6}alkyl groups include for instance trifluoromethyl and difluoromethyl.

The term "Het^1" as a group or part of a group is defined as a saturated or partially unsaturated monocyclic, bicyclic or tricyclic heterocycle having preferably 3 to 14 ring members, more preferably 5 to 10 ring members and more preferably 5 to 8 ring members, which contains one or more heteroatom ring members selected from nitrogen, oxygen or sulfur and which is optionally substituted on one or more carbon atoms by C_{1-6}alkyl, C_{1-6}alkyloxy, halogen, hydroxy, oxo, optionally mono- or disubstituted amino, nitro, cyano, haloC_{1-6}alkyl, carboxyl, C_{1-6}alkoxycarbonyl, C_{3-7}cycloalkyl, optionally mono- or disubstituted aminocarbonyl, optionally mono- or disubstituted aminoC_{1-6}alkyl, methylthio, methylsulfonyl, aryl and a saturated or partially unsaturated monocyclic, bicyclic or tricyclic heterocycle having 3 to 14 ring members which contains one or more heteroatom ring members selected from nitrogen, oxygen or sulfur and whereby the optional substituents on any amino function are independently selected from C_{1-6}alkyl, C_{1-6}alkylcarbonyl, C_{1-6}alkyloxy-A-, Het^2-A-, Het^2C_{1-6}alkyl, Het^2C_{1-6}alkyl-A-, Het^2oxy-A-, Het^2oxyC_{1-4}akyl-A-, aryl-A-, aryloxy-A-, aryloxyC_{1-4}alkyl-A-, arylC_{1-6}alkyl-A-, C_{1-6}alkyloxycarbonylamino-A-, amino-A-, aminoC_{1-6}alkyl and aminoC_{1-6}alkyl-A- whereby each of the amino groups may optionally be mono- or where possible di-substituted with C_{1-4}alkyl and whereby A is as defined above.

The term "Het^2" as a group or part of a group is defined as an aromatic monocyclic, bicyclic or tricyclic heterocycle having preferably 3 to 14 ring members, more preferably 5 to 10 ring members and more preferably 5 to 6 ring members, which contains one or more heteroatom ring members selected from nitrogen, oxygen or sulfur and which is optionally substituted on one or more carbon atoms by C_{1-6}alkyl,

C_{1-6}alkyloxy, halogen, hydroxy, optionally mono- or disubstituted amino, nitro, cyano, haloC_{1-6}alkyl, carboxyl, C_{1-6}alkoxycarbonyl, C_{3-7}cycloalkyl, optionally mono- or disubstituted aminocarbonyl, optionally mono- or disubstituted aminoC_{1-6}alkyl, methylthio, methylsulfonyl, aryl, Het^1 and an aromatic monocyclic, bicyclic or tricyclic heterocycle having 3 to 14 ring members; whereby the optional substituents on any amino function are independently selected from C_{1-6}alkyl, C_{1-6}alkylcarbonyl, C_{1-6}alkyloxy-A-, Het^1-A-, Het^1C_{1-6}alkyl, Het^1C_{1-6}alkyl-A-, Het^1oxy-A-, Het^1oxy-C_{1-4}akyl-A-, aryl-A-, aryloxy-A-, aryloxyC_{1-4}alkyl-A-, arylC_{1-6}alkyl-A-, C_{1-6}alkyloxy-carbonylamino-A-, amino-A-, aminoC_{1-6}alkyl and aminoC_{1-6}alkyl-A- whereby each of the amino groups may optionally be mono- or where possible di-substituted with C_{1-4}alkyl and whereby A is as defined above.

As used herein, the term (=O) forms a carbonyl moiety with the carbon atom to which it is attached.

As used herein before, the term "one or more" covers the possibility of all the available C-atoms, where appropriate, to be substituted, preferably, one, two or three.

When any variable (e.g. halogen or C_{1-4}alkyl) occurs more than one time in any constituent, each definition is independent.

The term "prodrug" as used throughout this text means the pharmacologically acceptable derivatives such as esters, amides and phosphates, such that the resulting *in vivo* biotransformation product of the derivative is the active drug as defined in the compounds of formula (I). The reference by Goodman and Gilman (The Pharmacological Basis of Therapeutics, 8th ed, McGraw-Hill, Int. Ed. 1992, "Biotransformation of Drugs", p 13–15) describing prodrugs generally is hereby incorporated. Prodrugs of a compound of the present invention are prepared by modifying functional groups present in the compound in such a way that the modifications are cleaved, either in routine manipulation or in vivo, to the parent compound. Prodrugs include compounds of the present invention wherein a hydroxy group, for instance the hydroxy group on the asymmetric carbon atom, or an amino group is bonded to any group that, when the prodrug is administered to a patient, cleaves to form a free hydroxyl or free amino, respectively.

Typical examples of prodrugs are described for instance in WO 99/33795, WO 99/33815, WO 99/33793 and WO 99/33792 all incorporated herein by reference.

Prodrugs are characterized by excellent aqueous solubility, increased bioavailability and are readily metabolized into the active inhibitors *in vivo*.

For therapeutic use, the salts of the compounds of formula (I) are those wherein the counterion is pharmaceutically or physiologically acceptable. However, salts having a pharmaceutically unacceptable counterion may also find use, for example, in the preparation or purification of a pharmaceutically acceptable compound of formula (I). All salts, whether pharmaceutically acceptable or not are included within the ambit of the present invention.

The pharmaceutically acceptable or physiologically tolerable addition salt forms which the compounds of the present invention are able to form can conveniently be prepared using the appropriate acids, such as, for example, inorganic acids such as hydrohalic acids, e.g. hydrochloric or hydrobromic acid; sulfuric; nitric; phosphoric and the like acids; or organic acids such as, for example, acetic, propanoic, hydroxyacetic, lactic, pyruvic, oxalic, malonic, succinic, maleic, fumaric, malic, tartaric, citric, methanesulfonic, ethanesulfonic, benzenesulfonic, *p*-toluenesulfonic, cyclamic, salicylic, *p*-amino-salicylic, pamoic and the like acids.

Conversely said acid addition salt forms can be converted by treatment with an appropriate base into the free base form.

The compounds of formula (I) containing an acidic proton may also be converted into their non-toxic metal or amine addition salt form by treatment with appropriate organic and inorganic bases. Appropriate base salt forms comprise, for example, the ammonium salts, the alkali and earth alkaline metal salts, e.g. the lithium, sodium, potassium, magnesium, calcium salts and the like, salts with organic bases, e.g. the benzathine, N-methyl, -D-glucamine, hydrabamine salts, and salts with amino acids such as, for example, arginine, lysine and the like.

Conversely said base addition salt forms can be converted by treatment with an appropriate acid into the free acid form.

The term "salts" also comprises the hydrates and the solvent addition forms which the compounds of the present invention are able to form. Examples of such forms are e.g. hydrates, alcoholates and the like.

The *N*-oxide forms of the present compounds are meant to comprise the compounds of formula (I) wherein one or several nitrogen atoms are oxidized to the so-called *N*-oxide.

The present compounds may also exist in their tautomeric forms. Such forms, although not explicitly indicated in the above formula are intended to be included within the scope of the present invention.

The term stereochemically isomeric forms of compounds of the present invention, as used hereinbefore, defines all possible compounds made up of the same atoms bonded by the same sequence of bonds but having different three-dimensional structures which are not interchangeable, which the compounds of the present invention may possess. Unless otherwise mentioned or indicated, the chemical designation of a compound encompasses the mixture of all possible stereochemically isomeric forms which said compound may possess. Said mixture may contain all diastereomers and/or enantiomers of the basic molecular structure of said compound. All stereochemically isomeric forms of the compounds of the present invention both in pure form or in admixture with each other are intended to be embraced within the scope of the present invention.

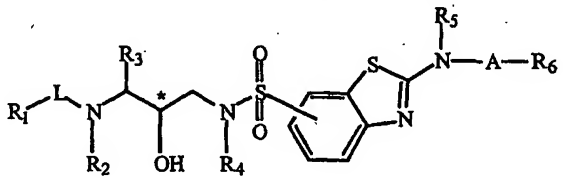
Pure stereoisomeric forms of the compounds and intermediates as mentioned herein are defined as isomers substantially free of other enantiomeric or diastereomeric forms of the same basic molecular structure of said compounds or intermediates. In particular, the term 'stereoisomerically pure' concerns compounds or intermediates having a stereoisomeric excess of at least 80% (i. e. minimum 90% of one isomer and maximum 10% of the other possible isomers) up to a stereoisomeric excess of 100% (i.e. 100% of one isomer and none of the other), more in particular, compounds or intermediates having a stereoisomeric excess of 90% up to 100%, even more in particular having a stereoisomeric excess of 94% up to 100% and most in particular having a stereoisomeric excess of 97% up to 100%. The terms 'enantiomerically pure' and 'diastereomerically pure' should be understood in a similar way, but then having regard to the enantiomeric excess, respectively the diastereomeric excess of the mixture in question.

Pure stereoisomeric forms of the compounds and intermediates of this invention may be obtained by the application of art-known procedures. For instance, enantiomers may be separated from each other by the selective crystallization of their diastereomeric salts with optically active acids. Alternatively, enantiomers may be separated by chromatographic techniques using chiral stationary phases. Said pure stereochemically isomeric forms may also be derived from the corresponding pure stereochemically isomeric forms of the appropriate starting materials, provided that the reaction occurs stereospecifically. Preferably, if a specific stereoisomer is desired, said compound will

be synthesized by stereospecific methods of preparation. These methods will advantageously employ enantiomerically pure starting materials.

The diastereomeric racemates of formula (I) can be obtained separately by conventional methods. Appropriate physical separation methods which may advantageously be employed are, for example, selective crystallization and chromatography, e.g. column chromatography.

It is clear to a person skilled in the art that the compounds of formula (I) contain at least one asymmetric center and thus may exist as different stereoisomeric forms. This asymmetric center is indicated with a asterisk (*) in the figure below.



The absolute configuration of each asymmetric center that may be present in the compounds of formula (I) may be indicated by the stereochemical descriptors R and S, this R and S notation corresponding to the rules described in Pure Appl. Chem. 1976, 45, 11-30. The carbon atom marked with the asterisk (*) preferably has the R configuration.

The present invention is also intended to include all isotopes of atoms occurring on the present compounds. Isotopes include those atoms having the same atomic number but different mass numbers. By way of general example and without limitation, isotopes of hydrogen include tritium and deuterium. Isotopes of carbon include C-13 and C-14.

Whenever used hereinafter, the term "compounds of formula (I)", or "the present compounds" or similar term is meant to include the compounds of general formula (I), their *N*-oxides, salts, stereoisomeric forms, racemic mixtures, prodrugs, esters and metabolites, as well as their quaternized nitrogen analogues.

A particular group of compounds are those compounds of formula (I) wherein one or more of the following restrictions apply :

R_1 is hydrogen, Het^1, Het^2, aryl, Het^1C_{1-6}alkyl, Het^2C_{1-6}alkyl, arylC_{1-6}alkyl, more in particular, R_1 is hydrogen, a saturated or partially unsaturated monocyclic or bicyclic heterocycle having 5 to 8 ring members, which contains one or more heteroatom ring members selected from nitrogen, oxygen or sulfur and which is optionally substituted, phenyl optionally substituted with one or more

substituents, an aromatic monocyclic heterocycle having 5 to 6 ring members, which contains one or more heteroatom ring members selected from nitrogen, oxygen or sulfur and which is optionally substituted on one or more carbon atoms, or C_{1-6}alkyl substituted with an aromatic monocyclic heterocycle having 5 to 6 ring members, which contains one or more heteroatom ring members selected from nitrogen, oxygen or sulfur and which is optionally substituted on one or more carbon atoms;

R_{11a} is H, alkyloxycarbonyl;

R_{11b} is C1-4 alkyl optionally substituted with aryl;

R_2 is hydrogen;

L is -C(=O)-, -O-C(=O)-,-O-C_{1-6}alkanediyl-C(=O)-, -NR_8-C_{1-6}alkanediyl-C(=O), more in particular, L is -C(=O)-, -O-C(=O)-,-O-CH_2-C(=O)-, whereby in each case the C(=O) group is attached to the NR_2 moiety;

R_3 is arylC_{1-4}alkyl, in particular, arylmethyl, more in particular phenylmethyl;

R_4 is optionally substituted C_{1-6}alkyl, in particular C_{1-6}alkyl optionally substituted with aryl, Het^1, Het^2, C_{3-7}cycloalkyl or amino optionally mono- or disubstituted where the substituents are selected from C_{1-4}alkyl, aryl, Het^1 and Het^2;

A is C_{1-6}alkanediyl, -C(=O)- or C_{1-6}alkanediyl-C(=O)-, in particular, A is methylene, 1,2-ethanediyl, 1,3-propanediyl, -C(=O)- or -CH_2-C(=O)-;

R_5 is hydrogen, C_{1-6}alkyl, Het^1C_{1-6}alkyl, aminoC_{1-6}alkyl whereby the amino group may optionally be mono- or di-substituted with C_{1-4}alkyl;

R_6 is C_{1-6}alkyloxy, Het^1, aryl, amino; and in case –A- is other than C_{1-6}alkanediyl then R^6 may also be C_{1-6}alkyl, Het^1C_{1-4}alkyl, aryloxyC_{1-4}alkyl or aminoC_{1-4}alkyl; whereby each of the amino groups may optionally be substituted; or

R^5 and –A-R^6 taken together with the nitrogen atom to which they are attached may also form Het^1.

A special group of compounds are those compounds of formula (I) wherein R_1 is Het^1, aryl, Het^2C_{1-6}alkyl; R_2 is hydrogen; L is -C(=O)-, -O-C(=O)-, -O-CH_2-C(=O)-, whereby in each case the C(=O) group is attached to the NR_2 moiety; R_3 is phenylmethyl; and R_4 is C_{1-6}alkyl.

Also a special group of compounds are those compounds of formula (I) wherein A is C_{1-6}alkanediyl or -C(=O)-; R_5 is hydrogen, methyl, Het^1C_{1-6}alkyl, aminoC_{1-6}alkyl whereby the amino group may optionally be mono- or di-substituted with C_{1-4}alkyl; R_6 is C_{1-6}alkyloxy, Het^1, amino; and in case –A- is other than C_{1-6}alkanediyl then R^6 may also be C_{1-6}alkyl, Het^1C_{1-4}alkyl or aminoC_{1-4}alkyl; whereby each of the amino groups may optionally be substituted.

An interesting group of compounds are those compounds of formula (I) wherein –A- is carbonyl and R_6 is aryl, Het^1C_{1-4}alkyl, aryloxyC_{1-4}alkyl or aminoC_{1-4}alkyl, whereby the amino groups may optionally be substituted; or –A- is carbonyl, R_6 is C_{1-4}alkyl and R_5 is Het^1C_{1-6}alkyl or aminoC_{1-6}alkyl whereby the amino group may optionally be mono- or di-substituted with C_{1-4}alkyl .

Another interesting group of compounds are those compounds of formula (I) wherein –A- is C_{1-6}alkanediyl and R_6 is amino and Het^1; whereby the amino group may optionally be mono- or di-substituted with C_{1-4}alkyl.

Another interesting group of compounds are those compounds of formula (I) wherein R_1 hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, arylC_{1-6}alkyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkylC_{1-6}alkyl, aryl, Het^1, Het^1C_{1-6}alkyl, Het^2, Het^2C_{1-6}alkyl; wherein Het^1 is a saturated or partially unsaturated monocyclic heterocycle having 5 or 6 ring members, which contains one or more heteroatom ring members selected from nitrogen, oxygen or sulfur and which is optionally substituted on one or more carbon atoms.

Another interesting group of compounds are those compounds of formula (I) wherein L is -O–C_{1-6}alkanediyl-C(=O)-.

Another interesting group of compounds are those compounds of formula (I) wherein

A is C_{1-6}alkanediyl, -C(=O)- or C_{1-6}alkanediyl-C(=O)-; whereby the point of attachment to the nitrogen atom is the C_{1-6}alkanediyl group in those moieties containing said group;

R_5 is hydrogen, C_{1-6}alkyl, Het^1C_{1-6}alkyl, Het^2C_{1-6}alkyl, aminoC_{1-6}alkyl whereby the amino group may optionally be mono- or di-substituted with C_{1-4}alkyl; and

in case –A- is –C(=O)- then R^6 is C_{1-6}alkyloxy, Het^1, Het^1oxy or Het^2oxy, aryl, Het^1C_{1-4}alkyl, Het^1oxyC_{1-4}alkyl, Het^2C_{1-4}alkyl, Het^2oxyC_{1-4}alkyl, arylC_{1-4}alkyl, aryloxyC_{1-4}alkyl or aminoC_{1-4}alkyl; and

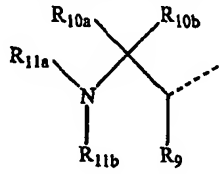
in case –A- is C_{1-6}alkanediyl then R^6 is amino, C_{1-6}alkyloxy, Het^1, Het^1oxy or Het^2oxy; and

in case –A- is C_{1-6}alkanediyl-C(=O)- then R^6 is C_{1-6}alkyloxy, Het^1, Het^1oxy or Het^2oxy, aryl, C_{1-6}alkyl, Het^1C_{1-4}alkyl, Het^1oxyC_{1-4}alkyl, Het^2C_{1-4}alkyl, Het^2oxyC_{1-4}alkyl, arylC_{1-4}alkyl, aryloxyC_{1-4}alkyl or aminoC_{1-4}alkyl;

whereby each of the amino groups in the definition of R_6 may optionally be substituted with one or more substituents selected from C_{1-4}alkyl, C_{1-4}alkylcarbonyl, C_{1-4}alkyloxycarbonyl, aryl, arylcarbonyl, aryloxycarbonyl, Het^1, Het^2, arylC_{1-4}alkyl, Het^1C_{1-4}alkyl or Het^2C_{1-4}alkyl; and

R^5 and $-A-R^6$ taken together with the nitrogen atom to which they are attached may also form Het^1 whereby Het^1 is substituted by at least an oxo group.

Interesting compounds are those wherein L is -O-C_{1-6}alkanediyl-C(=O)- or -NR_8-C_{1-6}-alkanediyl-C(=O)- and R_1 is a radical of formula



(II)

wherein

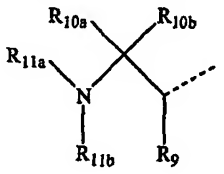
R_9 is oxo ,

R_{10a} and R_{10b} are, each independently, hydrogen or C_{1-4}alkyl optionally substituted with aryl, Het^1, Het^2, C_{1-4}alkyloxycarbonyl, carboxyl, aminocarbonyl, hydroxy, or amino optionally mono- or disubstituted where the substituents are selected from C_{1-4}alkyl,

R_{11a} is arylC_{1-4}alkyl, or C_{1-4}alkyl optionally substituted with aryl or halogen and

R_{11b} is hydrogen, or C_{1-6}alkyloxycarbonyl.

Also interesting compounds are those wherein L is -O-C_{1-6}alkanediyl-C(=O)- or -NR_8-C_{1-6}alkanediyl-C(=O)- and R_1 is a radical of formula



(II)

wherein

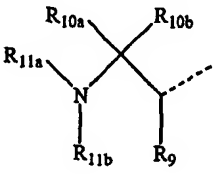
R_9 is oxo ,

R_{10a} and R_{10b} are hydrogen,

R_{11a} is arylC_{1-4}alkyl wherein the aryl group is substituted with a halogen and

R_{11b} is hydrogen, or C_{1-6}alkyloxycarbonyl.

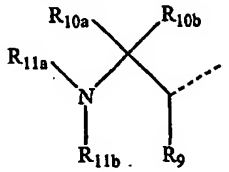
Other interesting compounds are those wherein L is -O-C_{1-6}alkanediyl-C(=O)- or -NR_8-C_{1-6}alkanediyl-C(=O)- and R_1 is a radical of formula



(II)

wherein R_9 is oxo , R_{10a} and R_{10b} are hydrogen, R_{11a} is *m*-fluorobenzyl and R_{11b} is hydrogen, or C_{1-6}alkyloxycarbonyl.

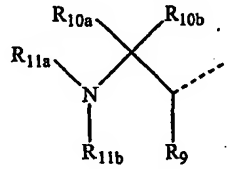
Yet other interesting compounds are those wherein L is -O-C_{1-6}alkanediyl-C(=O)- or -NR_8-C_{1-6}alkanediyl-C(=O)- and R_1 is a radical of formula



(II)

wherein R_9 is oxo, R_{10a} and R_{10b} are hydrogen, R_{11a} is *m*-fluorobenzyl and R_{11b} is hydrogen.

Other interesting compounds are those wherein L is -O-C_{1-6}alkanediyl-C(=O)- or -NR_8-C_{1-6}alkanediyl-C(=O)- and R_1 is a radical of formula



(II)

wherein R_9 is oxo, R_{10a} and R_{10b} are hydrogen, R_{11a} is *m*-fluorobenzyl and R_{11b} is tert-butyloxycarbonyl.

Interestingly, the compounds of the present invention may comprise chemically reactive moieties capable of forming covalent bonds to localized sites such that said compound have increased tissue retention and half-lives. The term "chemically reactive group" as used herein refers to chemical groups capable of forming a covalent bond. Reactive groups will generally be stable in an aqueous environment and will usually be carboxy, phosphoryl, or convenient acyl group, either as an ester or a mixed anhydride, or an imidate, or a maleimidate thereby capable of forming a covalent bond with functionalities such as an amino group, a hydroxy or a thiol at the target site on for example blood components.

Upon administration to an individual in need thereof, said compound is capable of forming covalent bonds to localized sites, with blood component for example, such that said compound according to the invention has increased tissue retention and half-lives. Usually, the covalent bond that is formed should be able to be maintained during the lifetime of the blood component, unless it is intended to be a release site. A major advantage of said new compound is the small amount of compound necessary to

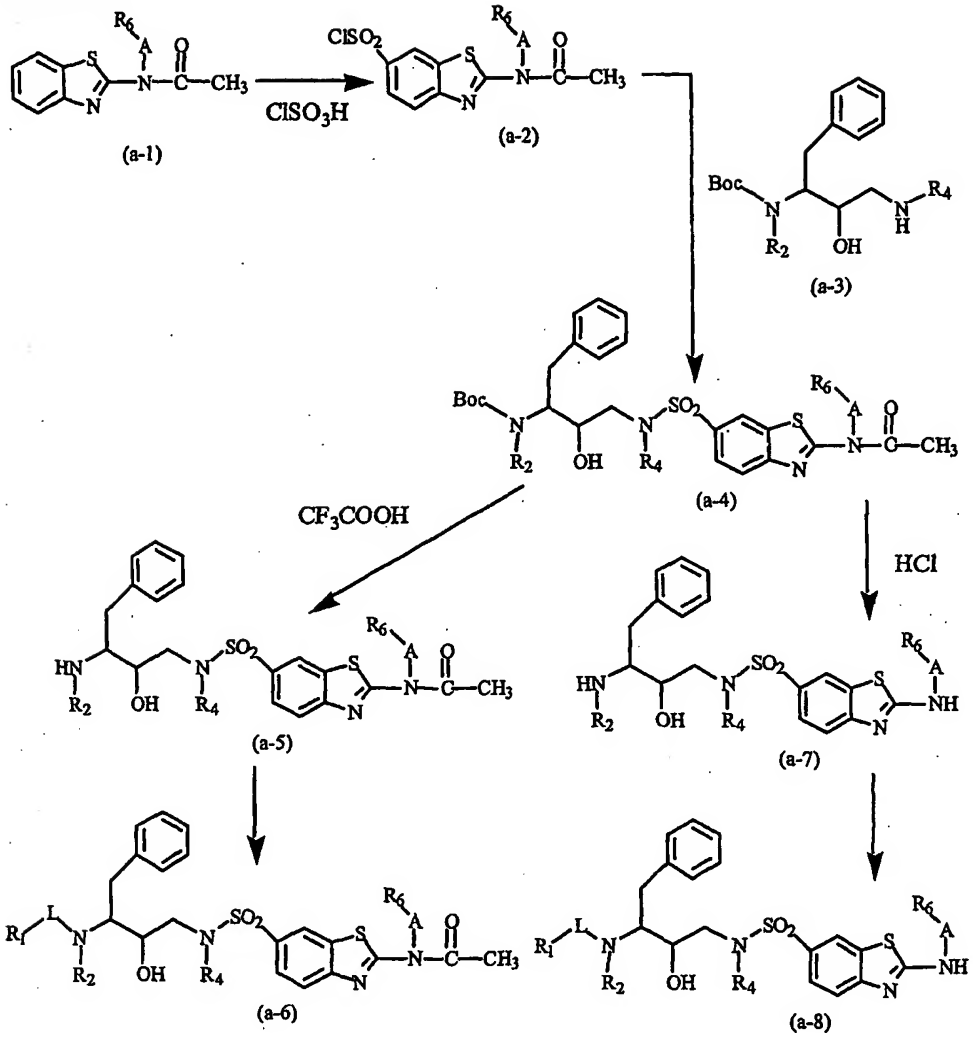
provide an effective effect. The reasons for this advantage are explained by the targeting of the delivery, the high yield of reaction between the reactive entity Y and reactive functionality and the irreversible nature of the bond formed after reaction. Furthermore, once bound to the membrane or tissue said compound according to the invention is not susceptible to liver metabolism, kidney filtration and excretion, and may even be protected from protease (inclusive of endopeptidase) activity which usually leads to loss of activity and accelerated elimination.

"Blood components" as used herein refers to either fixed or mobile blood components. Fixed blood components are non-mobile blood components and include tissues, membrane receptors, interstitial proteins, fibrin proteins, collagens, platelets, endothelial cells, epithelial cells and their associated membrane and membranous receptors, somatic body cells, skeletal and smooth muscle cells, neuronal components, osteocytes and osteoclasts and all body tissues especially those associated with the circulatory and lymphatic systems. Mobile blood components are blood components that do not have a fixed situs for any extended period of time, generally not exceeding 5, more usually one minute. These blood components are not membrane-associated and are present in the blood for extended periods of time and are present in a minimum concentration of at least 0.1 μg/ml. Mobile blood components include serum albumin, transferrin, ferritin and immunoglobulins such as IgM and IgG. The half-life of mobile blood components is at least about 12 hours.

The compounds of formula (I) can generally be prepared using procedures analogous to those procedures described in WO 95/06030, WO 96/22287, WO 96/28418, WO 96/28463, WO 96/28464, WO 96/28465 and WO 97/18205.

Particular reaction procedures to make the present compounds are described below. In the preparations described below,the reaction products may be isolated from the medium and, if necessary, further purified according to methodologies generally known in the art such as, for example, extraction, crystallization, trituration and chromatography.

Scheme A

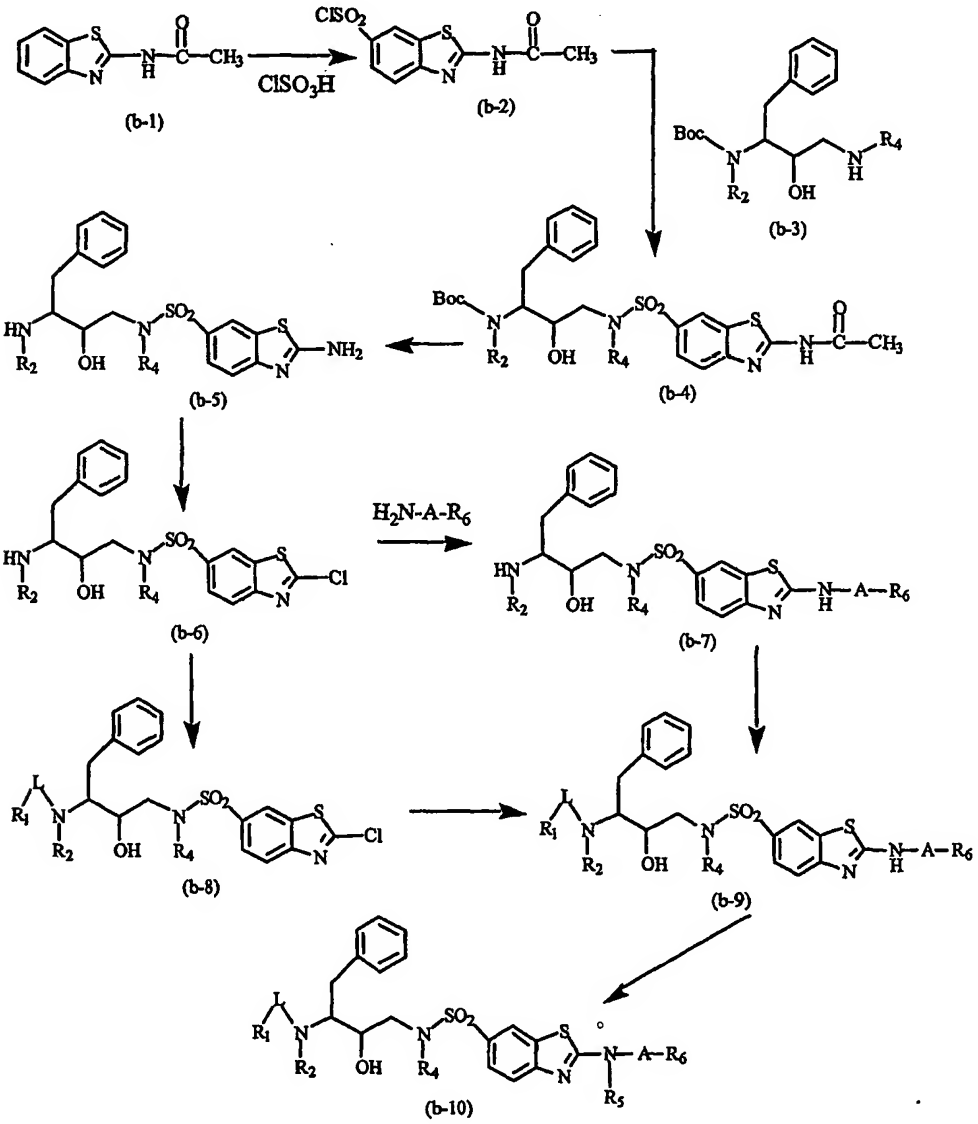


The 2-acetamido-6-chlorosulfonylbenzothiazole (intermediate **a-2**) was prepared following the procedure described in EP-A-0,445,926. Intermediates **a-4** were prepared by reacting an intermediate **a-3**, prepared according to the procedure described in WO97/18205 and also depicted in scheme F, with an intermediate **a-2** in a reaction-inert solvent such as dichloromethane, and in the presence of a base such as triethylamine and at low temperature, for example at 0 °C. The Boc group in the intermediate **a-3** is a protective *tert*-butyloxycarbonyl group. It may conveniently be replaced by another suitable protective group such as phtalimido or benzyloxycarbonyl. Using intermediate **a-4** as a starting material, intermediate **a-5** was deprotected using an acid such as trifluoroacetic acid in a suitable solvent such as dicloromethane. The resulting intermediate may be further reacted with an intermediate of formula R_1-L-(leaving group) in the presence of a base such as triethylamine and optionally in

the presence of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloric acid (EDC) or an alcohol such as *tert*-butanol, and in a suitable solvent such as dichloromethane; thus forming intermediates **a-6**. Particularly, intermediates of formula R_1-C(=O)-OH are suitable to further react with an intermediate **a-5**.

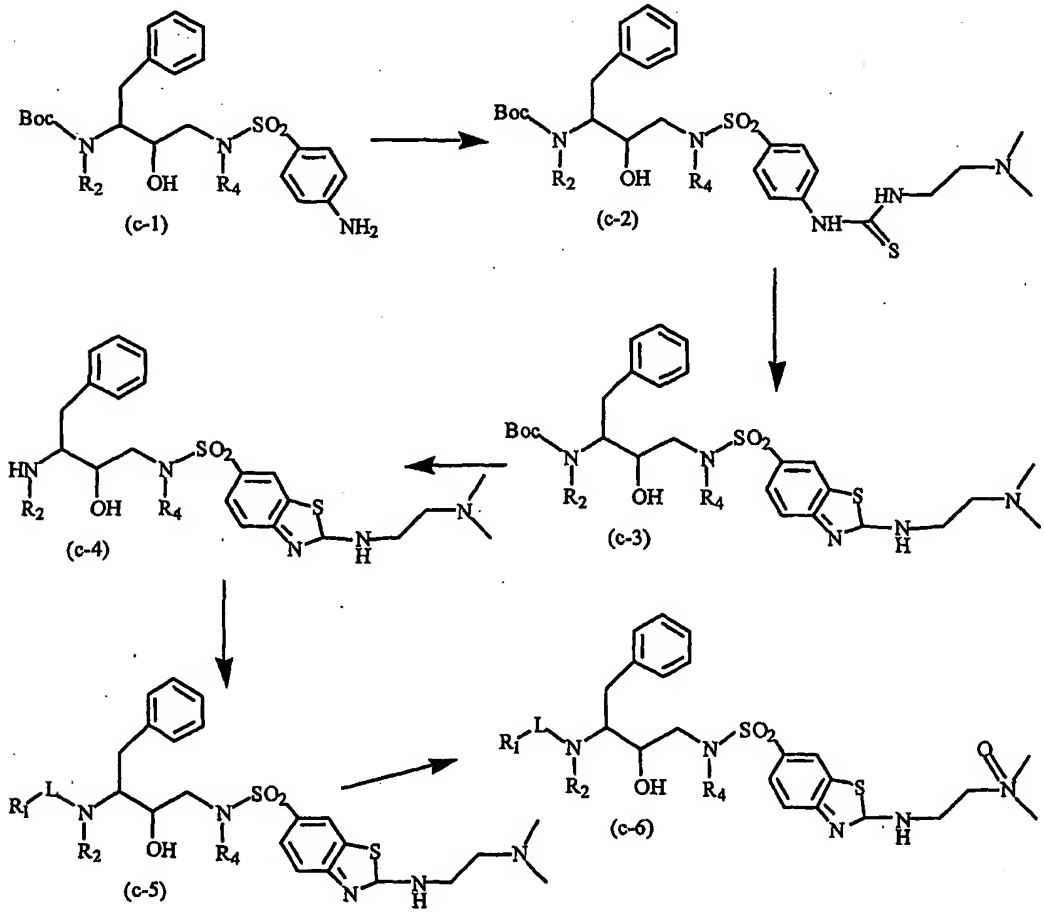
Alternatively, intermediates **a-4** may be deprotected with a strong acid such as hydrochloric acid in isopropanol, in a suitable solvent such as a mixture of ethanol and dioxane, thus preparing an intermediate **a-7**. Intermediates **a-8** can be prepared analogously to the procedure described for the preparation of intermediates **a-6**.

Scheme B



Intermediate **b-5** can be prepared according to the procedure described in scheme A. The aminobenzothiazole derivative **b-5** can be de-aminated by for instance treatment with sodium nitrite in combination with phosphoric acid, and subsequently with copper sulphate and sodium chloride, thus obtaining an intermediate **b-6**. Intermediate **b-6** may then be reacted with an intermediate of formula R_1-L-(leaving group) in the presence of a base such as triethylamine and optionally in the presence of EDC or an alcohol such as t-butanol, and in a suitable solvent such as dichloromethane, thus obtaining an intermediate **b-8**. Intermediate **b-8** may further be derivatized with an amine of formula H_2N-A-R_6 in a suitable solvent such as acetonitrile to obtain an intermediate **b-9**. Alternatively, intermediates **b-6** may first be reacted with H_2N-A-R_6 and then with formula R_1-L-(leaving group) as is shown in scheme B. Intermediate **b-9** can finally be further reacted with R_5COCl or a functional equivalent thereof in the presence of a base such as triethylamine and in a suitable solvent such as dichloromethane. Conveniently, said reaction is carried out under an inert atmosphere.

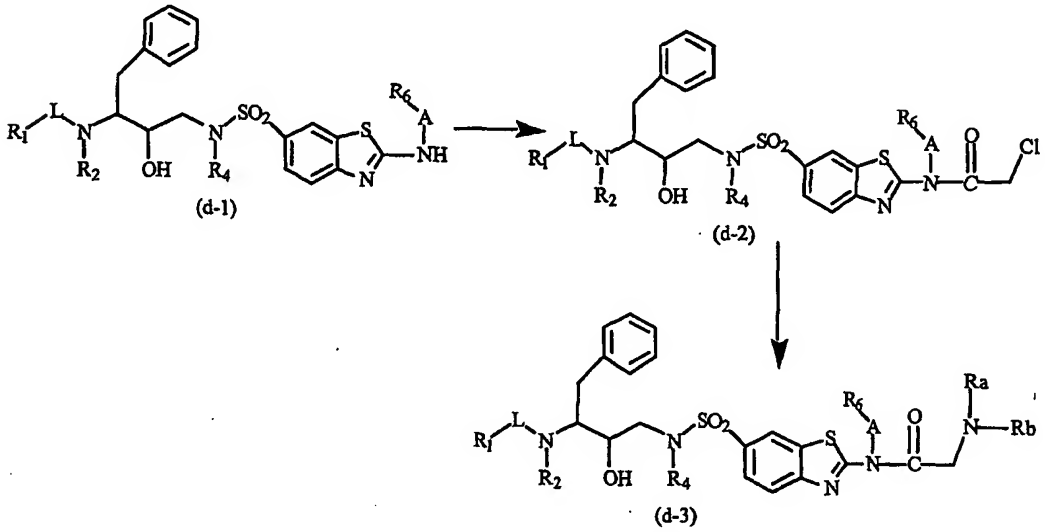
Scheme C



An alternative way of preparing compounds of formula (I) is exemplified in scheme C. Intermediate **c-1**, prepared according to the procedure described in US 6,140,505, was reacted with thiocarbonyldiimidazole in a reaction inert solvent such as tetrahydrofuran, and the resulting intermediate was further reacted with an amine such as for instance dimethylethylamine, thus obtaining the thiourea derivative **c-2**. Said intermediate **c-2** was then cyclized with bromine in the presence of an acid such as acetic acid, thus obtaining a benzthiazole derivative **c-3**. The following two steps in scheme C are analogous as those described for the preparation of intermediates **a-5** and **a-6** in scheme A. If so desired, intermediate **c-5** can be *N*-oxidized using for example meta chloroperbenzoic acid in dichloromethane.

A particular way of preparing acetamide substituted benzothiazoles is depicted in scheme D.

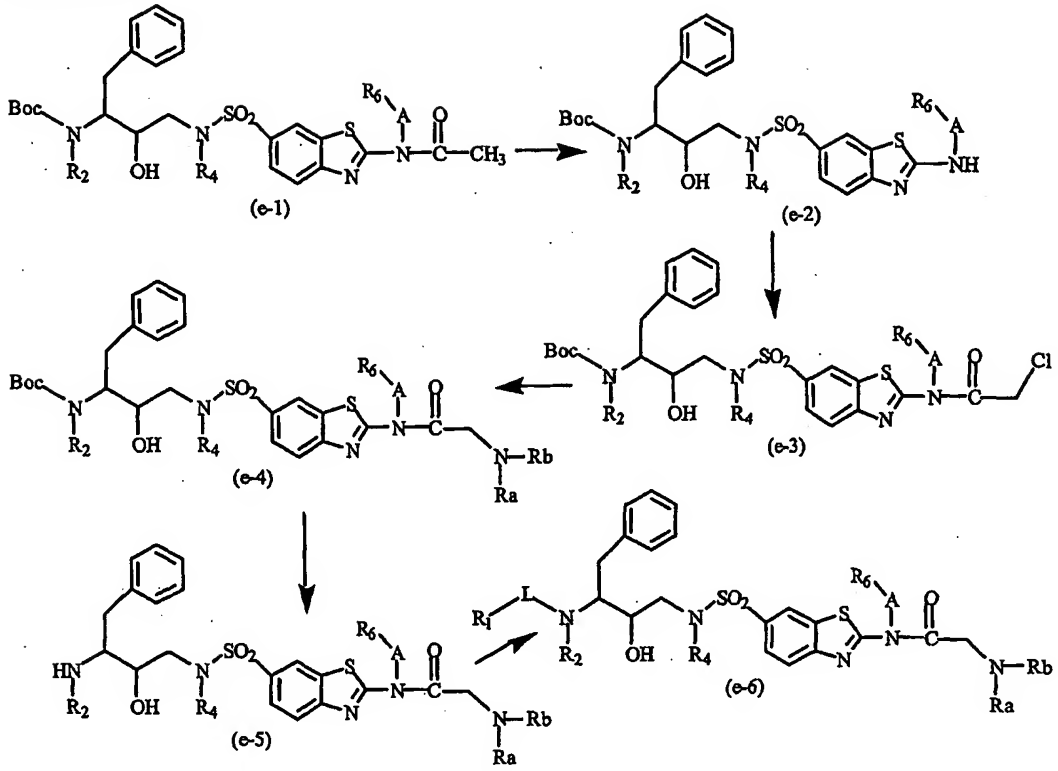
Scheme D



Intermediate **d-1**, prepared following the procedure as described in Scheme A, may be reacted with chloroacetylchloride, or a functional analogue, in the presence of a base such as triethylamine and in a solvent such as 1,4-dioxane in order to obtain an amide of formula **d-2**. Said intermediate **d-2** can further be reacted with an amine of formula NRaRb whereby Ra and Rb are defined as the possible substituents on an amino group in the variable R_6.

Another particular way of preparing acetamide substituted benzothiazoles is depicted in scheme E.

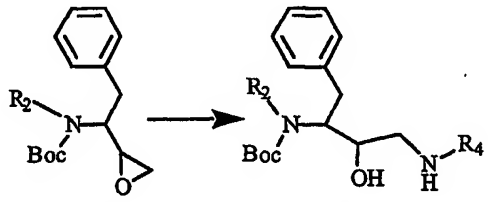
Scheme E



Intermediate **e-2** can be prepared by treating intermediate **e-1**, prepared following the procedure described in scheme A, with a base such as sodiumcarbonate in an aqueous medium such as a water dioxane mixture. The synthesis steps depicted in scheme E to obtain intermediate **e-6** are all analogous to reaction procedures described in the above synthesis schemes.

A number of intermediates and starting materials used in the foregoing preparations are known compounds, while others may be prepared according to art-known methodologies of preparing said or similar compounds.

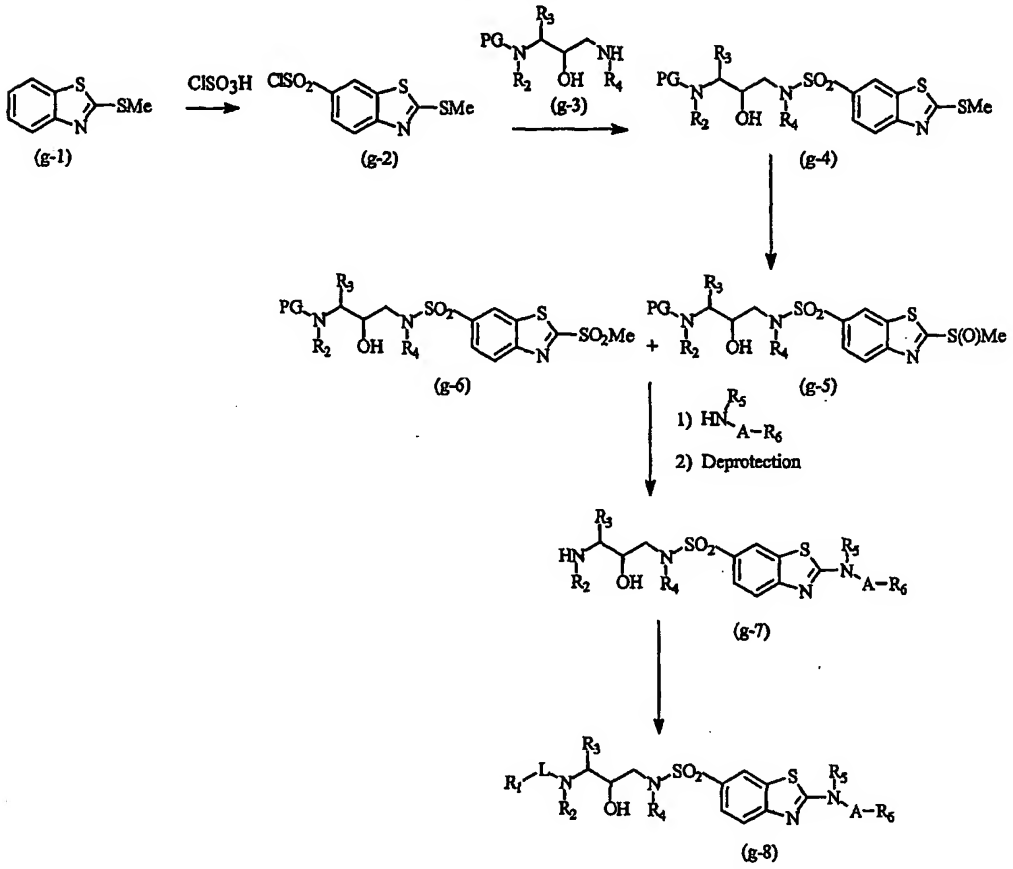
Scheme F



Intermediate **f-2**, corresponding to intermediate **a-3** in scheme A, may be prepared by adding an amine of formula H_2N-R_4 to an intermediate **f-1** in a suitable solvent such as isopropanol.

The compounds according to the present invention may also be prepared according to the method as depicted in scheme G.

Scheme G



The benzothiazole derivative **g-1** may be reacted with chlorosulfonic acid and subsequently treated with thionylchloride to yield intermediate **g-2.** Said intermediate **g-2** may be further reacted with intermediate **g-3** yielding an intermediate **g-4** wherein PG means a suitable protecting group such as for example Boc,. Said reaction may be performed in a suitable solvent such as for example 2-methyltetrahydrofuran and optionally in the presence of a suitable base such as triethylamine,

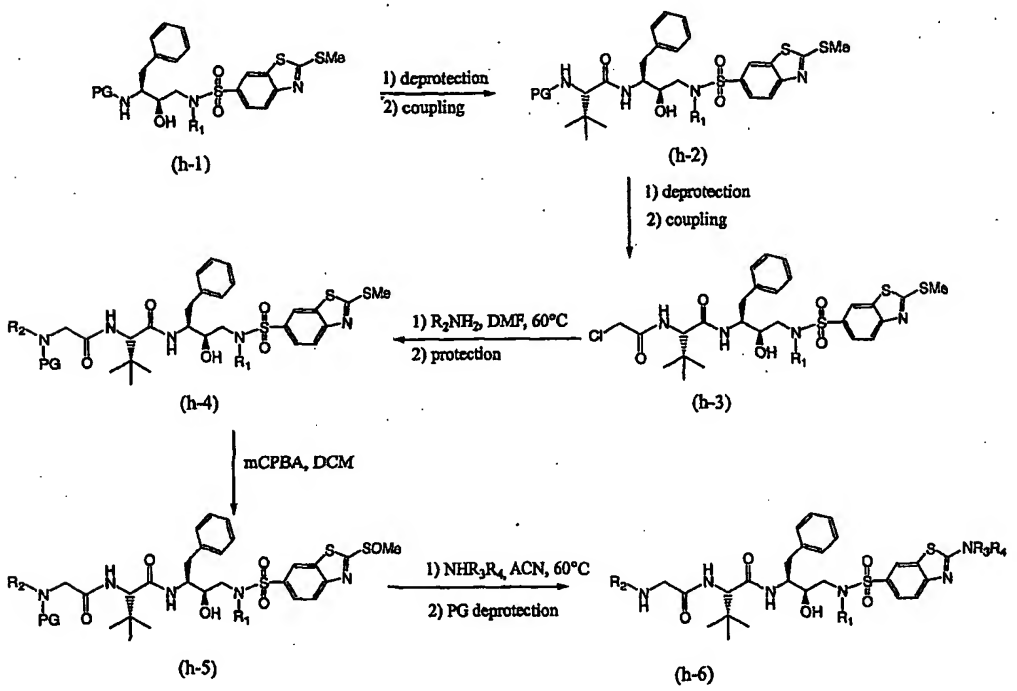
The intermediate **g-4** may then be reacted with a suitable reagent such as meta-chloroperoxybenzoic acid (mCPBA) or magnesium monoperoxyphtalate hexahydrate (MMPP) in the presence of a suitable solvent such as 2-methyltetrahydrofuran in ethanol thereby producing intermediates **g-5** and **g-6.**

Intermediates **g-5** and **g-6** may be further derivatized with a compound of formula $HN(R_5)A\text{-}R_6$ yielding intermediate **g-7** after a deprotection reaction. Intermediate **g-7**

may then be reacted with an intermediate of formula R_1-L-(leaving group) in the present of a base such as triethylamine and optionally in the presence of EDC or an alcohol such as t-butanol, and in a suitable solvent such as dichloromethane, thus obtaining the compound **g-8** which is compound of formula (I).

Another particular way of preparing some compounds according to the invention is depicted in scheme H.

Scheme H



After deprotection of the protective group of **h-1** using methods known in the art, such as HCl in isopropanol when PG is a Boc group, the free amine is reacted with a carboxylic acid , in the presence of a coupling agent such as EDC and HOBt, in an organic solvent such as dichloromethane, to yield **h-2**.

In one preferred embodiment, the carboxylic acid is the Boc-protected L-*tert*-Leucine.

h-2 is then deprotected as previously described and reacted with chloroacetic acid in the presence of EDC and HOBt, in dichloromethane, to give intermediate **h-3**, which is further substituted by a primary amine in an organic solvent such as dimethyl formamide (DMF), under heating conditions, then protected by an adequate protective group such as Boc, to give intermediate **h-4**.

Intermediate **h-4** is reacted with *meta*-chloroperoxybenzoic acid in dichloromethane to give the sulfoxide **h-5**, further substituted by an amine of formula NHR_3R_4 in an organic solvent such as acetonitrile, under heating conditions. The final compound **h-6** is obtained after removal of the protective group as previously described.

The compounds of formula (I) may also be converted to the corresponding *N*-oxide forms following art-known procedures for converting a trivalent nitrogen into its *N*-oxide form as is shown for instance for intermediate **c-6** in scheme C. Said *N*-oxidation reaction may generally be carried out by reacting the starting material of formula (I) with an appropriate organic or inorganic peroxide. Appropriate inorganic peroxides comprise, for example, hydrogen peroxide, alkali metal or earth alkaline metal peroxides, e.g. sodium peroxide, potassium peroxide; appropriate organic peroxides may comprise peroxy acids such as, for example, benzenecarboperoxoic acid or halo substituted benzenecarboperoxoic acid, e.g. 3-chloro-benzenecarboperoxoic acid, peroxoalkanoic acids, e.g. peroxoacetic acid, alkylhydroperoxides, e.g. *tert*-butyl hydroperoxide. Suitable solvents are, for example, water, lower alkanols, e.g. ethanol and the like, hydrocarbons, e.g. toluene, ketones, e.g. 2-butanone, halogenated hydrocarbons, e.g. dichloromethane, and mixtures of such solvents.

An interesting group of intermediates are those intermediates of formula **a-8**, **b-9** or **d-1** wherein $-A-R_6$ is hydrogen. Said intermediates may also have pharmacological properties similar to those pharmacological properties of the compounds of formula (I).

The present compounds can thus be used in animals, preferably in mammals, and in particular in humans as pharmaceuticals per se, in mixtures with one another or in the form of pharmaceutical preparations.

Furthermore, the present invention relates to pharmaceutical preparations which as active constituents contain an effective dose of at least one of the compounds of formula (I) in addition to customary pharmaceutically innocuous excipients and auxiliaries. The pharmaceutical preparations normally contain 0.1 to 90% by weight of a compound of formula (I). The pharmaceutical preparations can be prepared in a manner known per se to one of skill in the art. For this purpose, at least one of a compound of formula (I), together with one or more solid or liquid pharmaceutical excipients and/or auxiliaries and, if desired, in combination with other pharmaceutical active compounds, are brought into a suitable administration form or dosage form which can then be used as a pharmaceutical in human medicine or veterinary medicine.

Pharmaceuticals which contain a compound according to the invention can be administered orally, parenterally, e.g., intravenously, rectally, by inhalation, or topically, the preferred administration being dependent on the individual case, e.g., the particular course of the disorder to be treated. Oral administration is preferred.

The person skilled in the art is familiar on the basis of his expert knowledge with the auxiliaries which are suitable for the desired pharmaceutical formulation. Beside solvents, gel-forming agents, suppository bases, tablet auxiliaries and other active compound carriers, antioxidants, dispersants, emulsifiers, antifoams, flavor corrigents, preservatives, solubilizers, agents for achieving a depot effect, buffer substances or colorants are also useful.

Due to their favorable pharmacological properties, particularly their activity against multi-drug resistant HIV protease enzymes, the compounds of the present invention are useful in the treatment of individuals infected by HIV and for the prophylaxis of these individuals. In general, the compounds of the present invention may be useful in the treatment of warm-blooded animals infected with viruses whose existence is mediated by, or depends upon, the protease enzyme. Conditions which may be prevented or treated with the compounds of the present invention, especially conditions associated with HIV and other pathogenic retroviruses, include AIDS, AIDS-related complex (ARC), progressive generalized lymphadenopathy (PGL), as well as chronic CNS diseases caused by retroviruses, such as, for example HIV mediated dementia and multiple sclerosis.

The compounds of the present invention or any subgroup thereof may therefore be used as medicines against above-mentioned conditions. Said use as a medicine or method of treatment comprises the systemic administration to HIV-infected subjects of an amount effective to combat the conditions associated with HIV and other pathogenic retroviruses, especially HIV-1. Consequently, the compounds of the present invention can be used in the manufacture of a medicament useful for treating conditions associated with HIV and other pathogenic retroviruses, in particular medicaments useful for treating patients infected with multi-drug resistant HIV virus.

In a preferred embodiment, the invention relates to the use of a compound of formula (I) or any subgroup thereof in the manufacture of a medicament for treating or combating infection or disease associated with multi-drug resistant retrovirus infection in a mammal, in particular HIV-1 infection. Thus, the invention also relates to a method of treating a retroviral infection, or a disease associated with multi-drug

resistant retrovirus infection comprising administering to a mammal in need thereof an effective amount of a compound of formula (I) or a subgroup thereof.

In another preferred embodiment, the present invention relates to the use of formula (I) or any subgroup thereof in the manufacture of a medicament for inhibiting a protease of a multi-drug resistant retrovirus in a mammal infected with said retrovirus, in particular HIV-1 retrovirus.

In another preferred embodiment, the present invention relates to the use of formula (I) or any subgroup thereof in the manufacture of a medicament for inhibiting multi-drug resistant retroviral replication, in particular HIV-1 replication.

The compounds of the present invention may also find use in inhibiting ex vivo samples containing HIV or expected to be exposed to HIV. Hence, the present compounds may be used to inhibit HIV present in a body fluid sample which contains or is suspected to contain or be exposed to HIV.

Also, the combination of an antiretroviral compound and a compound of the present invention can be used as a medicine. Thus, the present invention also relates to a product containing (a) a compound of the present invention, and (b) another antiretroviral compound, as a combined preparation for simultaneous, separate or sequential use in treatment of retroviral infections, in particular, in the treatment of infections with multi-drug resistant retroviruses. Thus, to combat or treat HIV infections, or the infection and disease associated with HIV infections, such as Acquired Immunodeficiency Syndrome (AIDS) or AIDS Related Complex (ARC), the compounds of this invention may be co-administered in combination with for instance, binding inhibitors, such as, for example, dextran sulfate, suramine, polyanions, soluble CD4; fusion inhibitors, such as, for example, T20, T1249, SHC-C, PRO542; co-receptor binding inhibitors, such as, for example, AMD 3100 (Bicyclams), TAK 779; RT inhibitors, such as, for example, foscarnet and prodrugs, MIV-310; nucleoside RTIs, such as, for example, AZT, 3TC, DDC, DDI, D4T, Abacavir, FTC, DAPD, dOTC; nucleotide RTIs, such as, for example, PMEA, PMPA, tenofovir; NNRTIs, such as, for example, nevirapine, delavirdine, efavirenz, 8 and 9-Cl TIBO (tivirapine), loviride, TMC-125, TMC-120, MKC-442, UC 781, Capravirine, DPC 961, DPC963, DPC082, DPC083, calanolide A, SJ-3366, TSAO, 4"-deaminated TSAO; RNAse H inhibitors, such as, for example, SP1093V, PD126338; TAT inhibitors, such as, for example, RO-5-3335, K12, K37; integrase inhibitors, such as, for example, L 708906, L 731988; protease inhibitors, such as, for example, amprenavir, ritonavir, nelfinavir, saquinavir, indinavir, lopinavir, BMS 232632, BMS 186316, DPC 681, DPC 684,

tipranavir, AG1776, DMP 450, L 756425, PD178390, PNU 140135; glycosylation inhibitors, such as, for example, castanospermine, deoxynojirimycine.

The combination may provide a synergistic effect, whereby viral infectivity and its associated symptoms may be prevented, substantially reduced, or eliminated completely.

The compounds of the present invention may also be administered in combination with immunomodulators (e.g., bropirimine, anti-human alpha interferon antibody, IL-2, methionine enkephalin, interferon alpha, and naltrexone) antibiotics (e.g., pentamidine isothiorate) , vaccines or hormones (e.g growth hormone) to ameliorate, combat, or eliminate HIV infection and its symptoms.

For an oral administration form, compounds of the present invention are mixed with suitable additives, such as excipients, stabilizers or inert diluents, and brought by means of the customary methods into the suitable administration forms, such as tablets, coated tablets, hard capsules, aqueous, alcoholic, or oily solutions. Examples of suitable inert carriers are gum arabic, magnesia, magnesium carbonate, potassium phosphate, lactose, glucose, or starch, in particular, corn starch. In this case the preparation can be carried out both as dry and as moist granules. Suitable oily excipients or solvents are vegetable or animal oils, such as sunflower oil or cod liver oil. Suitable solvents for aqueous or alcoholic solutions are water, ethanol, sugar solutions, or mixtures thereof. Polyethylene glycols and polypropylene glycols are also useful as further auxiliaries for other administration forms.

For subcutaneous or intravenous administration, the active compounds, if desired with the substances customary therefor such as solubilizers, emulsifiers or further auxiliaries, are brought into solution, suspension, or emulsion. The compounds of formula (I) can also be lyophilized and the lyophilizates obtained used, for example, for the production of injection or infusion preparations. Suitable solvents are, for example, water, physiological saline solution or alcohols, e.g. ethanol, propanol, glycerol, in addition also sugar solutions such as glucose or mannitol solutions, or alternatively mixtures of the various solvents mentioned.

Suitable pharmaceutical formulations for administration in the form of aerosols or sprays are, for example, solutions, suspensions or emulsions of the compounds of formula (I) or their physiologically tolerable salts in a pharmaceutically acceptable solvent, such as ethanol or water, or a mixture of such solvents. If required, the formulation can also additionally contain other pharmaceutical auxiliaries such as

surfactants, emulsifiers and stabilizers as well as a propellant. Such a preparation customarily contains the active compound in a concentration from approximately 0.1 to 50%, in particular from approximately 0.3 to 3% by weight.

In order to enhance the solubility and/or the stability of the compounds of formula (I) in pharmaceutical compositions, it can be advantageous to employ α-, β- or γ-cyclodextrins or their derivatives. Also co-solvents such as alcohols may improve the solubility and/or the stability of the compounds of formula (I) in pharmaceutical compositions. In the preparation of aqueous compositions, addition salts of the subject compounds are obviously more suitable due to their increased water solubility.

Appropriate cyclodextrins are α-, β- or γ-cyclodextrins (CDs) or ethers and mixed ethers thereof wherein one or more of the hydroxy groups of the anhydroglucose units of the cyclodextrin are substituted with C_{1-6}alkyl, particularly methyl, ethyl or isopropyl, e.g. randomly methylated β-CD; hydroxyC_{1-6}alkyl, particularly hydroxyethyl, hydroxypropyl or hydroxybutyl; carboxyC_{1-6}alkyl, particularly carboxymethyl or carboxyethyl; C_{1-6}alkylcarbonyl, particularly acetyl; C_{1-6}alkyloxycarbonylC_{1-6}alkyl or carboxyC_{1-6}alkyloxyC_{1-6}alkyl, particularly carboxymethoxypropyl or carboxyethoxypropyl; C_{1-6}alkylcarbonyloxyC_{1-6}alkyl, particularly 2-acetyloxypropyl. Especially noteworthy as complexants and/or solubilizers are β-CD, randomly methylated β-CD, 2,6-dimethyl-β-CD, 2-hydroxyethyl-β-CD, 2-hydroxyethyl-γ-CD, 2-hydroxypropyl-γ-CD and (2-carboxymethoxy)propyl-β-CD, and in particular 2-hydroxypropyl-β-CD (2-HP-β-CD).

The term mixed ether denotes cyclodextrin derivatives wherein at least two cyclodextrin hydroxy groups are etherified with different groups such as, for example, hydroxy-propyl and hydroxyethyl.

An interesting way of formulating the present compounds in combination with a cyclodextrin or a derivative thereof has been described in EP-A-721,331. Although the formulations described therein are with antifungal active ingredients, they are equally interesting for formulating the compounds of the present invention. The formulations described therein are particularly suitable for oral administration and comprise an antifungal as active ingredient, a sufficient amount of a cyclodextrin or a derivative thereof as a solubilizer, an aqueous acidic medium as bulk liquid carrier and an alcoholic co-solvent that greatly simplifies the preparation of the composition. Said formulations may also be rendered more palatable by adding pharmaceutically acceptable sweeteners and/or flavors.

Other convenient ways to enhance the solubility of the compounds of the present invention in pharmaceutical compositions are described in W0-94/05263, PCT application No. PCT/EP98/01773, EP-A-499,299 and WO 97/44014, all incorporated herein by reference.

More in particular, the present compounds may be formulated in a pharmaceutical composition comprising a therapeutically effective amount of particles consisting of a solid dispersion comprising (a) a compound of formula (I), and (b) one or more pharmaceutically acceptable water-soluble polymers.

The term "a solid dispersion" defines a system in a solid state (as opposed to a liquid or gaseous state) comprising at least two components, wherein one component is dispersed more or less evenly throughout the other component or components. When said dispersion of the components is such that the system is chemically and physically uniform or homogenous throughout or consists of one phase as defined in thermodynamics, such a solid dispersion is referred to as "a solid solution". Solid solutions are preferred physical systems because the components therein are usually readily bioavailable to the organisms to which they are administered.

The term "a solid dispersion" also comprises dispersions which are less homogenous throughout than solid solutions. Such dispersions are not chemically and physically uniform throughout or comprise more than one phase.

The water-soluble polymer in the particles is conveniently a polymer that has an apparent viscosity of 1 to 100 mPa.s when dissolved in a 2 % aqueous solution at 20°C solution.

Preferred water-soluble polymers are hydroxypropyl methylcelluloses or HPMC. HPMC having a methoxy degree of substitution from about 0.8 to about 2.5 and a hydroxypropyl molar substitution from about 0.05 to about 3.0 are generally water soluble. Methoxy degree of substitution refers to the average number of methyl ether groups present per anhydroglucose unit of the cellulose molecule. Hydroxy-propyl molar substitution refers to the average number of moles of propylene oxide which have reacted with each anhydroglucose unit of the cellulose molecule.

The particles as defined hereinabove can be prepared by first preparing a solid dispersion of the components, and then optionally grinding or milling that dispersion.

Various techniques exist for preparing solid dispersions including melt-extrusion, spray-drying and solution-evaporation, melt-extrusion being preferred.

It may further be convenient to formulate the present compounds in the form of nanoparticles which have a surface modifier adsorbed on the surface thereof in an amount sufficient to maintain an effective average particle size of less than 1000 nm. Useful surface modifiers are believed to include those which physically adhere to the surface of the antiretroviral agent but do not chemically bond to the antiretroviral agent.

Suitable surface modifiers can preferably be selected from known organic and inorganic pharmaceutical excipients. Such excipients include various polymers, low molecular weight oligomers, natural products and surfactants. Preferred surface modifiers include nonionic and anionic surfactants.

Yet another interesting way of formulating the present compounds involves a pharmaceutical composition whereby the present compounds are incorporated in hydrophilic polymers and applying this mixture as a coat film over many small beads, thus yielding a composition with good bioavailability which can conveniently be manufactured and which is suitable for preparing pharmaceutical dosage forms for oral administration.

Said beads comprise (a) a central, rounded or spherical core, (b) a coating film of a hydrophilic polymer and an antiretroviral agent and (c) a seal-coating polymer layer.

Materials suitable for use as cores in the beads are manifold, provided that said materials are pharmaceutically acceptable and have appropriate dimensions and firmness. Examples of such materials are polymers, inorganic substances, organic substances, and saccharides and derivatives thereof.

Another aspect of the present invention concerns a kit or container comprising a compound of formula (I) in an amount effective for use as a standard or reagent in a test or assay for determining the ability of a potential pharmaceutical to inhibit HIV protease, HIV growth, or both. This aspect of the invention may find its use in pharmaceutical research programs.

The compounds of the present invention can be used in high-throughput target-analyte assays such as those for measuring the efficacy of said compound in HIV treatment.

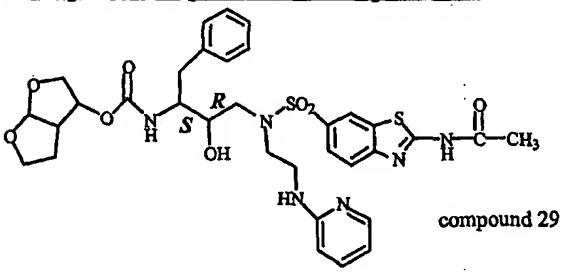
The compounds of the present invention can be used in phenotypic resistance monitoring assays, such as known recombinant assays, in the clinical management of resistance developing diseases such as HIV. A particularly useful resistance monitoring system is a recombinant assay known as the Antivirogram™. The Antivirogram™ is a highly automated, high throughput, second generation, recombinant assay that can measure susceptibility, especially viral susceptibility, to the compounds of the present invention. (Hertogs K, de Bethune MP, Miller V *et al.* *Antimicrob Agents Chemother*, 1998; 42(2):269-276, incorporated by reference).

The dose of the present compounds or of the physiologically tolerable salt(s) thereof to be administered depends on the individual case and, as customary, is to be adapted to the conditions of the individual case for an optimum effect. Thus it depends, of course, on the frequency of administration and on the potency and duration of action of the compounds employed in each case for therapy or prophylaxis, but also on the nature and severity of the infection and symptoms, and on the sex, age, weight and individual responsiveness of the human or animal to be treated and on whether the therapy is acute or prophylactic. Customarily, the daily dose of a compound of formula (I) in the case of administration to a patient approximately 75 kg in weight is 1 mg to 1g, preferably 3 mg to 0.5 g. The dose can be administered in the form of an individual dose, or divided into several, e.g. two, three, or four, individual doses.

Experimental Part

Preparation of the compounds of formula (I) and their intermediates

Example 1 : Preparation of compound 29



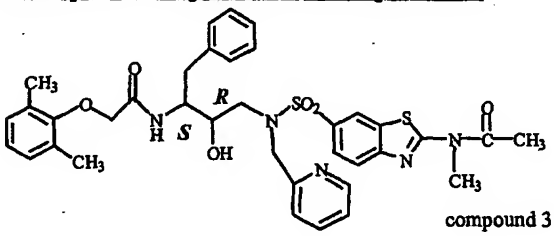
compound 29

A mixture of 1.56 g of intermediate a-3 (R_2= H and R_4 = -CH_2-CH_2-NH-(2-pyridinyl)) and 0.59 g of triethylamine in 50 ml of dichloromethane was stirred at 0°C. Then 1.25 g of 2-(acetylamino)-6-benzothiazolesulfonyl chloride, was added and the reaction mixture stirred overnight at room temperature. After washing with water, the organic layer was separated, dried and the solvent evaporated. The brown solid obtained was re-dissolved in methanol at 70°C, cooled and filtered off, yielding 1.9 g (75 %) of intermediate a-4 (R_2 = H, R_4 = -CH_2-CH_2-NH-(2-pyridinyl) and –A-R_6 = H).

To a mixture of 6 g of intermediate **a-4** (R_2 = H, R_4 = -CH_2-CH_2-NH-(2-pyridinyl) and -A-R_6 = H) in 50 ml of dichloromethane, 7.3 ml of trifluoracetic acid were added. The reaction mixture was stirred at room temperature for 6 hours. Extra dichloromethane was added and washed with $NaHCO_3$ solution. The organic layer was dried and the solvent evaporated under reduced pressure, yielding 4.1 g (81%) of intermediate **a-5** (R_2 = H, R_4 = -CH_2-CH_2-NH-(2-pyridinyl) and –A-R_6 = H).

A mixture of 0.60 g of intermediate **a-5** (R_2 = H, R_4 = -CH_2-CH_2-NH-(2-pyridinyl) and -A-R_6 = H), 0.29 g of 1-[[[[(3S,3aR,6aS)+(3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-yl]oxy]carbonyl]oxy]- 2,5-pyrrolidinedione (prepared analogously to the procedure described in WO9967417) and 0.33g of triethylamine in 15 ml of dichloromethane was stirred at room temperature for 24 hours. Solvents were evaporated and the solid obtained was redissolved in methanol at 70°C, cooled and filtered off, yielding 0.53 g (69%) of compound 29. Mass Spectral data : m/z = 711 (M+H)

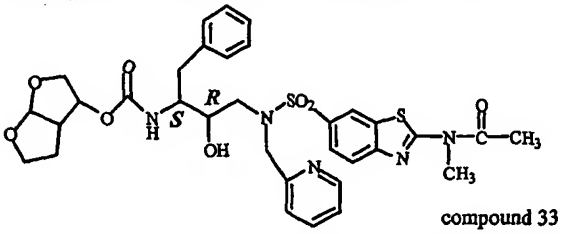
Example 2 : Preparation of compound 31



compound 31

A mixture of 540 mg of intermediate **a-5** (R_2 = H, R_4 = -CH_2-(2-pyridinyl) and –A-R_6 = H), 135 mg of *tert*-butanol, 192 mg of EDC and 101 mg of triethylamine in 5 ml of dichloromethane, was stirred overnight at room temperature. The reaction mixture was then washed with a Na_2CO_3 solution and brine. The organic layer was separated, dried and the solvent evaporated. The residue was purified by preparative-HPLC, yielding 184 mg (26%) of compound 31. Mass spectral data : m/z = 702 (M+H)

Example 3 : Preparation of compound 33

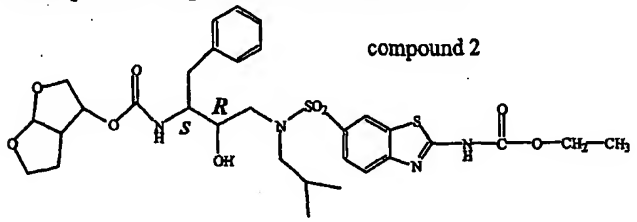


compound 33

A mixture of 540 mg of intermediate **a-5** (R_2 = H, R_4 = -CH_2-(2-pyridinyl) and –A-R_6 = H), 271 mg of 1-[[[[(3S,3aR,6aS)+(3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-yl]oxy]carbonyl]oxy]- 2,5-pyrrolidinedione and 101 mg of triethylamine in 5 ml of

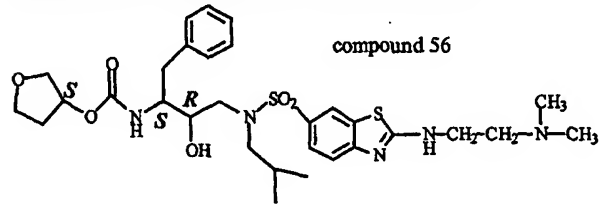
dichloromethane was stirred at room temperature for 24 hours. The reaction mixture was then washed with a Na_2CO_3 solution and brine. The organic layer was separated, dried and the solvent evaporated. The residue was purified by preparative-HPLC, yielding 161 mg (23%) of compound 33. Mass spectral data : m/z = 696 (M+H)

Example 4 : Preparation of compound 2



To a mixture of 0.3g of racemic intermediate **a-8** (R_2= H, R_4= isobutyl, –A-R_6 = H and –L-R_1 = [[hexahydrofuro[2,3-b]furan-3-yl]oxy]carbonyl) and 0.061g triethylamine in anhydrous dioxane is added in several portions 0.18g ethyl chloroformate. The reaction mixture was heated overnight to 60°C. To the mixture is added 10ml water and 0.4g potassium carbonate followed by 2 hours of stirring. Dioxane was removed in vacuo. The aqueous phase was extracted with dichloromethane. The combined organic phase was concentrated and the obtained residue purified by chromatography yielded 0.23g (68%) of compound 2.

Example 5 : Preparation of compound 56



A mixture of 19.66 g of [2R-hydroxy-3-[(2-methylpropyl)amino]-1S-(phenylmethyl)-propyl]-carbamic acid, 1,1-dimethylethyl ester (described in WO97/18205) and 17.76 g of triethylamine in 200 ml of dichloromethane is stirred at 0°C for 20 minutes under inert atmosphere. 18.72 g of 2-(acetylamino)-6-benzothiazolesulfonyl chloride was added in small portions and the mixture was then stirred at room temperature for 2 hours. After washing with 5% HCl solution, saturated sodium bicarbonate solution and brine, the organic layer was dried and the solvent evaporated under reduced pressure. The crude product was purified on silica gel eluting with 4% methanol in dichloromethane yielding 30.82 g (90%) of intermediate **b-4** (R_2= H and R_4= isobutyl).

To a mixture of 13.75 g of intermediate **b-4** (R_2= H and R_4= isobutyl) in 130 ml of ethanol/dioxane (1:1) 65 ml of HCl (5 to 6 N in isopropanol) was added. The reaction

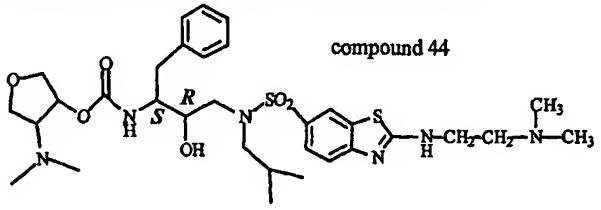
was stirred at 50°C for 22 hours. After evaporating, the salt was treated with saturated sodium bicarbonate solution and extracted with dichloromethane. The organic layer was dried, the solvent evaporated and the residue purified on silica gel eluting with 3% methanol in dichloromethane yielding 18.36 g (72%) of intermediate **b-5** (R_2= H and R_4= isobutyl).

A solution of 1.81 g of sodium nitrite in 10 ml of water was added over a 40-min period to a mixture of 9.80 g of intermediate **b-5** (R_2= H and R_4= isobutyl) in 180 ml of 85% phosphoric acid held at –10°C. After being stirred for 1.5 hour, the mixture was added to a stirred solution of 10.90 g of copper sulphate pentahydrate and 12.67 g of sodium chloride in 80 ml of water at –10°C. The mixture was stirred for 1.5 hour , being allowed to warm to room temperature, and then made alkaline (pH = 8) with an ammonium hydroxide solution under cooling. The resulting solution was extracted with ethylacetate. After drying and evaporating the solvent, 7.59 g (74%) of intermediate **b-6** (R_2= H and R_4= isobutyl) was obtained.

A mixture of 1.63g of intermediate **b-6** (R_2= H and R_4= isobutyl), 0.80 g of 1-[[[[(3S)-tetrahydro-3-furanyl]oxy]carbonyl]oxy]-2,5-pyrrolidinedione and 0.53 g of triethylamine in 50 ml of dichloromethane was stirred at room temperature for 5 hours. After evaporation of dichloromethane under reduced pressure, the crude product was purified on silica gel eluting with 3% of methanol in dichloromethane yielding 0.58 g (29%) of intermediate **b-8** (R_2= H, R_4= isobutyl, R_1-L- = [[(3S)-tetrahydro-3-furanyl]oxy]carbonyl).

To a solution of 0.23 g of intermediate **b-8** (R_2= H, R_4= isobutyl, R_1-L- = [[(3S)-tetrahydro-3-furanyl]oxy]carbonyl) in 30 ml of acetonitrile was added 0.20 g of *N,N*-dimethylethylenediamine. This solution was stirred at 80°C for 4 hours. After evaporation of acetonitrile under reduced pressure, the crude product was purified on silica gel eluting with 2% of methanol in dichloromethane yielding 0.12 g (50%) of compound 56. Mass spectral data : m/z = 634 (M+H)

Example 6 : Preparation of compound 44



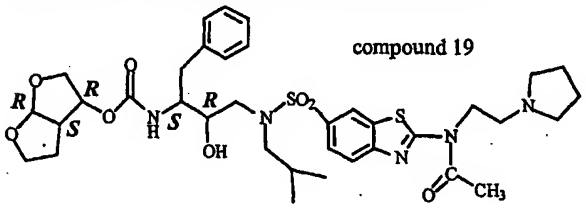
To a solution of 0.90 g of intermediate **b-6** (R_2= H and R_4= isobutyl) in 20 ml of acetonitrile was added 0.85 g of N,N-dimethylethylenediamine. This solution was

stirred at 80°C for 3 hours. After evaporation of acetonitrile under reduced pressure, the product was washed with 2% sodium carbonate and extracted with ethylacetate. The organic layer was dried, the solvent evaporated under reduced pressure and purified on silica gel eluting with 1% of ammonia in dichloromethane, yielding 0.57 g (58%) of intermediate **b-7** (R_2= H, R_4= isobutyl and –A-R_6 = $CH_2CH_2N(CH_3)_2$).

A mixture of 0.65 g of (± *trans*)- 4-(dimethylamino)tetrahydro-3-furanol (synthesis described in US 3,265,711), 3.78 g of disuccinimidyl carbonate and 1.50 g of triethylamine in 30 ml of dichloromethane was stirred at room temperature for 24 hours. After washing the resulting solution with saturated sodium bicarbonate, the organic layer was dried and the solvent evaporated under reduced pressure to give 0.52 g (38%) of (± *trans*)-1-[[[[4-(dimethylamino)-tetrahydro-furan-3-yl]oxy]-carbonyl]oxy]-2,5-pyrrolidinedione.

A mixture of 0.25g of intermediate **b-7** (R_1 = H, R_2 = $CH_2CH_2N(Me)_2$), 0.13 g (± *trans*)-1-[[[[4-(dimethylamino)-tetrahydro-furan-3-yl]oxy]carbonyl]oxy]-2,5-pyrrolidinedione and 0.07 g of triethylamine in 15 ml of dichloromethane was stirred at room temperature for 24 hours. After evaporation of dichloromethane under reduced pressure, the crude product was purified on silica gel eluting with 4% of ammonia in dichloromethane, yielding 0.14 g (43%) of compound 44. Mass spectral data : m/z = 677 (M+H)

Example 7 : Preparation of compound 19



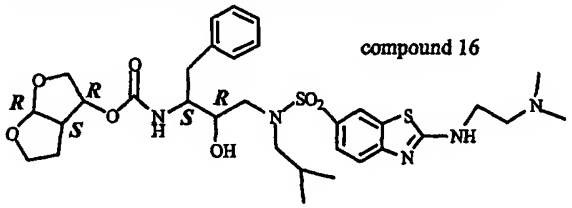
To a solution of 0.83 g of intermediate **b-6** (R_2= H and R_4= isobutyl) in 20 ml of acetonitrile was added 0.40 g of N-(2-aminoethyl)-pyrrolidine. This solution was stirred at 80°C for 4 hours. After evaporation of acetonitrile under reduced pressure, the product was washed with 2% sodium carbonate and extracted with ethylacetate. The organic layer was dried, evaporated under reduced pressure and purified on silica gel eluting with 1% of ammonia in dichloromethane, yielding 0.47 g (49%) of intermediate **b-7** (R_2= H, R_4= isobutyl and –A-R_6 = CH_2CH_2-(1-pyrrolidinyl)).

A mixture of 0.47g of intermediate **b-7** (R_2= H, R_4= isobutyl and –A-R_6 = CH_2CH_2-(1-pyrrolidinyl)) 0.24 g of 1-[[[[(3R,3aS,6aR)-hexahydrofuro[2,3-*b*]furan-3-yl]oxy]-carbonyl]oxy]- 2,5-pyrrolidinedione and 0.10 g of triethylamine in 20 ml of

dichloromethane was stirred at room temperature for 24 hours. After evaporation of dichloromethane under reduced pressure, the crude product was purified on silica gel eluting with 2% of ammonia in dichloromethane, yielding 0.54 g (88%) of intermediate **b-9** (R_2= H, R_4= isobutyl, –A-R_6 = CH_2CH_2-(1-pyrrolidinyl) and –L-R_1 = [[(3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-yl]oxy]carbonyl).

To a solution of 0.54 g of intermediate **b-9** (R_2= H, R_4= isobutyl, –A-R_6 = CH_2CH_2-(1-pyrrolidinyl) and –L-R_1 = [[(3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-yl]oxy]–carbonyl) and 0.16 g of triethylamine in 40 ml of dichloromethane under inert atmosphere was added 0.22 g of acetyl chloride. After stirring at room temperature for 2 hours and washing with water, the organic layer was dried and evaporated under reduced pressure to give 0.50 g (87%) of compound 19. Mass spectral data : m/z = 744 (M+H)

Example 8 : Preparation of compound 16



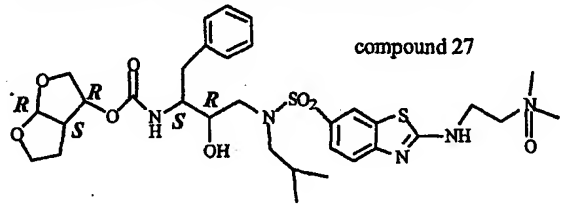
To a solution of 4.91 g of [(1S,2R)-3-[[(4-aminophenyl)sulfonyl](2-methylpropyl)–amino]-2-hydroxy-1-(phenylmethyl)propyl]-carbamic acid, 1,1-dimethylethyl ester (prepared as described in US 6,140,505) in 40 ml of anhydrous tetrahydrofuran, was added 1.78 g of 1,1'-thiocarbonyldiimidazole. This solution was refluxed 4 hours. After cooled at 25°C, 0.88 g of N,N-dimethylethylamine was added and then this solution was again refluxed 16 hours. After cooling at 25°C, evaporation of tetrahydrofuran under reduced pressure, dichloromethane was added, washed with water, the organic phase was dried and concentrated. This crude product was purified on silica gel eluting with 5% of methanol in dichloromethane, yielding 3.8 g (62%) of intermediate **c-2** (R_2= H, R_4= isobutyl). Mass spectral data : m/z = 622 (M+H), 566, 532.

To a solution of 2.5 g of the intermediate **c-2** (R_2= H, R_4= isobutyl) in 10 ml of acetic acid was added a solution of 0.64g of bromine in 10ml acetic acid. After 2 hours, this crude product was concentrated, dichloromethane added and this organic phase washed with a saturated potassium carbonate solution. The organic phase was dried on magnesium sulfate, filtered and concentrated, yielding intermediate **c-3** (R_2= H, R_4= isobutyl). Mass spectral data : m/z = 620 (M+H), 564, 520, 261.

The intermediate **c-3** (R_2= H, R_4= isobutyl) was diluted with 20 ml of dichloromethane and 5 ml of trifuoroacetic acid were added. This solution was stirred for 1 hour and then concentrated. This residue was washed with a potassium carbonate solution and extracted with dichloromethane. This crude material was purified on silica gel eluting with 5% of methanol in dichloromethane yielding 1.5 g (72%) of the intermediate **c-4** (R_2= H, R_4= isobutyl).

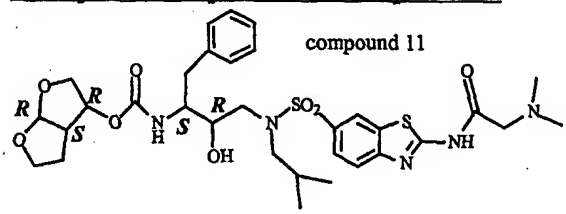
1.5 g of the intermediate **c-4** (R_2= H, R_4= isobutyl), 0.81 g of 1-[[[[(3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-yl]oxy]carbonyl]oxy]-2,5-pyrrolidinedione 0.67 g of triethylamine in 5 ml of dichloromethane was stirred for 4 hours at room temperature. This crude product was directly purified on silica gel eluting with 5% methanol in dichloromethane, yielding 0.80 g (39%) of compound 16.

Example 9 : Preparation of compound 27



To 0.34 g of compound 16 in 5ml of dichloromethane was added 0.08g of sodium bicarbonate and 0.15g (75%) of meta chloroperbenzoic acid. This solution was stirred 2 hours at room temperature. Water was added and the residue was extracted with dichloromethane. The organic phase was dried on magnesium sulfate, filtered and concentrated. This crude material was purified on silica gel eluting with 5% of methanol in dichloromethane yielding 0.09 g (26%) of compound 27. Mass spectral data : m/z = 692 (M+H)

Example 10 : Preparation of compound 11



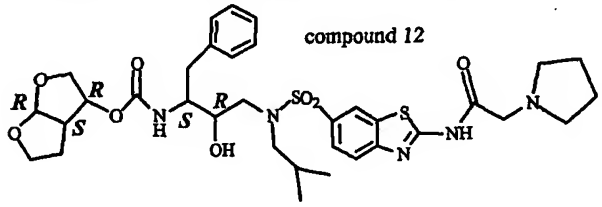
To a mixture of 2.32g 2-amino-N-[(2R,3S)-3-amino-2-hydroxy-4-phenylbutyl]-N-(2-methylpropyl)-6-benzothiazolesulfonamide and 1.0g triethylamine in dichloromethane was added 1.47g 1-[[[[(3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-yl]oxy]carbonyl]-oxy]- 2,5-pyrrolidinedione. After overnight stirring the reaction mixture was washed with a saturated sodium bicarbonate solution, dried over magnesium sulfate, filtered

and concentrated. The obtained residue was purified by column (dichloromethane:methanol 95:5) to afford 2.76g intermediate **d-1** (R_2= H, R_4= isobutyl, –A-R_6 = H and –L-R_1 = [[(3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-yl]oxy]carbonyl) (88%).

To a mixture of intermediate **d-1** (R_2= H, R_4= isobutyl, –A-R_6 = H and –L-R_1 = [[(3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-yl]oxy]carbonyl) (2.0g; 3.3 mmole) and triethylamine (1.16g; 11.5 mmole) in dry 1,4-dioxane is added chloroacetylchloride (429 mg; 3.8 mmole). The resulting mixture was stirred at rt for 3 hours. Another portion of chloroacetylchloride (180mg; 1.5 mmole) was added and stirring was continued for 3 hours. After evaporation of the solvent the residue was purified by chromatography (dichloromethane:methanol 98:2) to afford 1.57 g (70%) of intermediate **d-2** (R_2= H, R_4= isobutyl, –A-R_6 = H and –L-R_1 = [[(3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-yl]oxy]carbonyl). Mass spectral data : (ES+): 681/683(M+H).

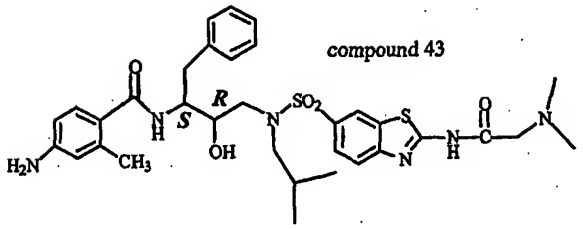
To a solution of the intermediate **d-2** (R_2= H, R_4= isobutyl, –A-R_6 = H and –L-R_1 = [[(3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-yl]oxy]carbonyl) (0.45g; 0.66 mmole) in tetrahydrofuran was added 4.6ml of an 40% wt aqueous dimethylamine solution. After stirring for two hours tetrahydrofuran was evaporated. The aqueous layer was extracted with dichloromethane. The combined organic layers were dried over magnesium sulfate. Concentration in vacuo yielded 0.42g (92%) of compound 11. Mass spectral data : (ES+): 690 (M+H), 560.

Example 11 : Preparation of compound 12



To a solution of the intermediate **d-2** (R_2= H, R_4= isobutyl, –A-R_6 = H and –L-R_1 = [[(3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-yl]oxy]carbonyl) in dichloromethane was 1.5 eq. of pyrrolidine together with sodium carbonate as a base. After overnight stirring at room temperature the solvent was removed in vacuo. The residue was purified by chromatography (dichloromethane:methanol) to yield 76% of compound 12. Mass spectral data : (ES+) 715 (M+H)

Example 12 : Preparation of compound 43



A mixture of 6.13g of intermediate **e-1** (R_2= H, R_4= isobutyl and –A-R_6 = H) and 10g sodium carbonate in water/dioxane (1/2) was heated to 80°C for 48 hours. Dioxane was removed in vacuo. The resulting aqueous phase was extracted twice with ethyl acetate. After drying over magnesium sulfate and filtration the combined organic phase was concentrated to yield 5.08g of intermediate **e-2** (R_2= H, R_4= isobutyl and –A-R_6 = H). Mass spectral data (ES+): 549(M+H), 449.

To a mixture of 3.0g 2-aminobenzothiazole intermediate **e-2** (R_2= H, R_4= isobutyl and –A-R_6 = H) and 1.1g triethylamine in dry 1,4-dioxane was added 0.77g chloroacetyl-chloride. The resulting mixture was stirred overnight. After evaporation of the solvent the residue was purified by chromatography (dichloromethane:methanol 98:2) to afford 2.7g (78%) of intermediate **e-3** (R_2= H, R_4= isobutyl and –A-R_6 = H). Mass spectral data (ES+): 625/627(M+H).

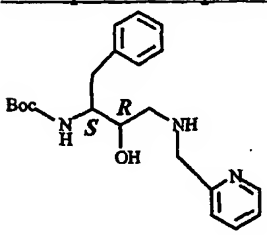
To a solution of 0.8g intermediate **e-3** (R_2= H, R_4= isobutyl and –A-R_6 = H) in tetrahydrofuran was added 8 ml of an 40% wt aqueous dimethylamine solution. After stirring for three hours tetrahydrofuran was evaporated. The aqueous layer was extracted with dichloromethane. The combined organic layers were dried over magnesium sulfate. Concentration in vacuo provided 0.58g (85%) of intermediate **e-4** (R_2= H, R_4= isobutyl, –A-R_6 = H and R_a=R_b =CH_3). Mass spectral data (ES+): 634(M+H), 534.

To a solution of intermediate **e-4** (R_2= H, R_4= isobutyl, –A-R_6 = H and R_a=R_b =CH_3) in dichloromethane was added trifluoracetic acid (10 equivalents). After overnight stirring the organic phase was washed with saturated sodium bicarbonate and brine, dried over magnesium sulfate, filtered and concentrated to afford the intermediate **e-5** (R_2= H, R_4= isobutyl, –A-R_6 = H and R_a=R_b =CH_3).

To a solution of 0.35g 4-amino-2-methylbenzoic acid in dichloromethane was added at 0°C 0.09g 1-hydroxybenzotriazole and 0.13g EDC. After one half hour of stirring the temperature was allowed to rise to room temperature and stirring was continued for one more hour. After addition of the intermediate **e-5** (R_2= H, R_4= isobutyl, –A-R_6 = H and R_a=R_b =CH_3) the reaction mixture was stirred at room temperature for two days. Then

the solvent was removed in vacuo and the obtained residue was purified by chromatography (dichloromethane:methanol 97:3) to afford 0.12g (29%) of compound 43. Mass spectral data (ES+): 667(M+H).

Example 13 : Preparation of the intermediate f-2 (R_2= H and R_4= -CH_2-(2-pyridinyl))

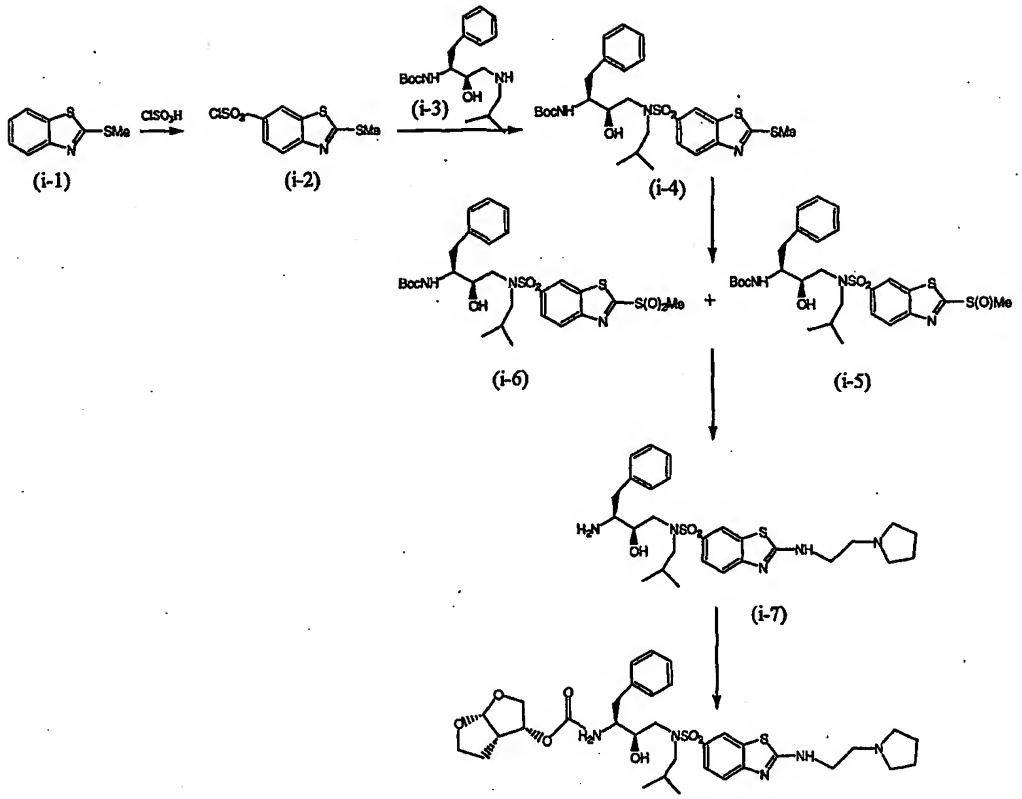


25 g of 2-pyridylmethylamine was stirred at reflux in 400 ml of isopropanol. Then a solution of 21 g of the 2S,3S-1,2-epoxy-3-(*tert*-butoxycarbonylamino)-4-phenylbutane, commercially available, in 200 ml of isopropanol was added dropwise. The reaction mixture was stirred overnight at reflux. After evaporation of the solvent, the residue was redissolved in dichloromethane and washed 4 times with water. The organic layer was dried and evaporated. The residue obtained was purified by chromatography (dichloromethane:7N NH_3 in methanol, 98:2) to afford 24 g (84%) of intermediate f-2 (R_2= H and R_4= -CH_2-(2-pyridinyl)).

Example 14 : Preparation of compound 20

Compound 20 may also be prepared according to the method depicted in scheme G. The specific method is illustrated hereunder in scheme I.

Scheme I



Chlorosulfonic acid (0.193 kg; 1.65 mol) was stirred at 10°C under nitrogen. **i-1** was added carefully. The reaction mixture was stirred for 3 hours at 90°C. The heating was stopped and thionylchloride (0.079 kg; 0.66 mol) was added slowly. The reaction mixture was stirred for another hour at 90°C. The reaction mixture was cooled until 35°C and then 200 ml ethylacetate was added slowly. Another 200 ml of ethylacetate was added quickly after the beginning of the product precipitation. The precipitate was filtered and washed twice with 200 ml ethylacetate and twice with 1000 ml cold water. The precipitate was then stirred in a $NaHCO_3$ solution until pH = 7. This mixture was filtered and the white solid **i-2** was dried in a vacuum oven at 50°C. (0.123 kg, 80%). (LC/MS MW^+; 280,282)

A mixture of 0.120 kg (0.36 mol) of intermediate **i-3** and 0.073 kg (0.72 mol) of triethylamine in 2-methyltetrahydrofuran (1.150 kg) was stirred at 35 °C until dissolution of the reactants. Then 0.100 kg (0.36 mol) of intermediate **i-2** was added and the reaction mixture was stirred for 1.5 hours at 55°C. After washing the reaction mixture with water (0.500 kg), the organic layer was separated and washed with 0.500

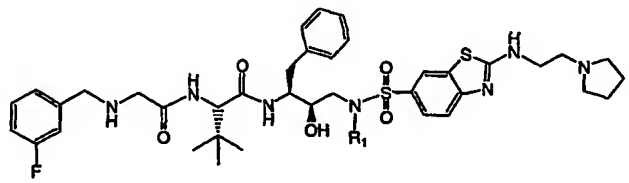
kg 1.5 N HCl solution. Then the organic layer was separated, dried and evaporated yielding **i-4**; 0.208 kg (100%). (LC/MS MW^+; 480,481,482)

0.208 kg (0.36 mol) of intermediate **i-4** was stirred in a mixture of 1 kg 2-methyltetrahydrofuran, 0.060 kg H_2O and 0.110 kg ethanol at 40°C until dissolution of all the reactants. Then magnesium monoperoxyphtalate hexahydrate 0.200 kg (0.4 mol) was added. The mixture was stirred and heated for 15 min at 60°C. The reaction mixture was made alkaline with 0.400 kg Na_2CO_3 until pH = 10. Intermediates **i-5** and **i-6**. (about 70% **i-5** and 30% **i-6**). (LC/MS MW^+ **i-5**; 496,497,498 MW^+ **i-6**; 511,513) To this reaction mixture was added at 60°C 0.050 kg (0.43 mol) N-(2-aminoethylpyrrolidine. This mixture was stirred for 20 hours at 70°C. Then the slurry was cooled to 40°C and HCl concentrated (12N) was added dropwise until pH = 7-8. A phase precipitation was then observed. The organic layer was separated, evaporated and dried in the vacuum oven at 50°C yielding Boc N-protected **i-7**; 0.217 kg (93%). (LC/MS MW^+; 646,647,648)

0.217 kg (0.36 mol) of intermediate Boc N-protected **i-7** was dissolved in 1.4 kg isopropanol at 50°C. Then 0.370 L HCl 5 à 6 N (2 mol) was added and the mixture was heated and stirred for 2.5 hours at 70°C. This hot reaction mixture was added dropwise to 0.50 kg cold (0°C-15°C) isopropanol. The precipitate was filtered and washed with diisopropyl ether. The slightly brown solid was triturated in a DIPE/toluene (50/50) mixture and then filtered and dried in the vacuum oven at 50°C, yielding 0.170 kg (76%) of **i-7** HCl-salt. (LC/MS MW^+; 546,547,548).

A mixture of 1.3g of intermediate **i-7** ,0.774 g of 1-[[[[(3S,3aR,6aS)+(3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-yl]oxy]carbonyl]oxy]- 2,5-pyrrolidinedione (prepared analogously to the procedure described in WO9967417) and 0.33g of triethylamine in 100 ml of dichloromethane was stirred at room temperature for 24 hours. This crude product was wahed with NaHCO3 solution. The organic layer was dried and the solvant evaporated under reduced pressure. The residue was purified on silica gel, yielding 0.74g (45%) of compound 20. Mass spectra data : m/z=702(M+H).

Example 15 : Preparation of the compound 85 and its intermediates R_1 = isobutyl)



This compound was prepared following the procedure depicted in scheme H.

11 g of intermediate **h-1** (PG = Boc, R_1 = isobutyl) [(1S,2R)-2-hydroxy-3-[(2-methylpropyl)[[2-(methylthio)-benzothiazol-6-yl]sulfonyl]amino]-1-(phenyl methyl)propyl]carbamic acid, 1,1-dimethylethyl ester were dissolved in 300 mL of HCl in isopropanol and 100 mL of dichloromethane and the solution was stirred at room temperature overnight. The reaction mixture was then concentrated and treated with a mixture of dichloromethane and sodium hydroxide in water. The organic layer was then dried over $MgSO_4$ and evaporated to give 8.8 g (97%) of the deprotected intermediate N-[(2R,3S)-3-amino-2-hydroxy-4-phenylbutyl]-N-(2-methylpropyl)[2-(methylthio)-benzothiazol-6-yl]sulfonamide, as a free base. Mass spectral data : m/z = 480 (M+H).

4.15 g of the previous intermediate, 2 g of Boc-L-*tert*-Leucine, 1.17 g of HOBt and 1.66 g of EDC were dissolved in 150 mL of dichloromethane and stirred at room temperature overnight. The reaction mixture was then successively washed with a solution of NaHCO3 in water, brine, dried over $MgSO_4$ and evaporated to give 6 g (100 %) of intermediate **h-2** [(1S)-1-[[[(1S,2R)-2-hydroxy-3-[(2-methylpropyl)[(2-(methylthio)-benzothiazol-6-yl)sulfonyl]amino]-1-(phenylmethyl)propyl]amino]-carbonyl]-2,2-dimethylpropyl]carbamic acid, 1,1-dimethylethyl ester. Mass spectral data : m/z = 693 (M+H).

6 g of intermediate **h-2** were dissolved in 100 mL of HCl in isopropanol, and stirred at room temperature during 2h. The reaction mixture was then concentrated and treated with a mixture of dichloromethane and a solution of sodium carbonate in water. The organic phase was then washed with brine, dried over $MgSO_4$ and evaporated to give 3.9 g (76%) of the deprotected intermediate as a free base. Mass spectral data : m/z = 593 (M+H).

3.9 g of the previous intermediate, 0.69 g of chloroacetic acid, 0.98 g of HOBt, and 1.38 g of EDC were dissolved in 100 mL of dichloromethane and stirred at RT overnight. The reaction mixture was then washed with brine, dried over $MgSO_4$ and evaporated. The crude compound was purified on silica gel eluting with 0 to 5% methanol in dichloromethane, yielding 3.72 g (85%) of the desired intermediate **h-3** 2-[(chloroacetyl)amino]-3,3-dimethyl-N-[(1S,2R)-2-hydroxy-3-[(2-methylpropyl)[[2-(methylthio)-benzothiazol-6-yl]sulfonyl]amino]-1-(phenylmethyl)propyl]-(2S)-butanamide. Mass spectral data : m/z = 669 (M+H).

3.72 g of intermediate **h-3** and 1.27 mL of meta-fluorobenzylamine were dissolved in DMF and stirred at 60°C during 2h. The reaction mixture was then concentrated and treated with a mixture of dichloromethane and a solution of sodium carbonate in water.

The organic phase was then dried over $MgSO_4$ and evaporated to yield 4.3 g (100%) of the desired intermediate N'-[(3-fluorophenyl)methyl]glycyl-N-[(1S,2R)-2-hydroxy-3-[(2-methylpropyl)[[2-(methylthio)benzothiazol-6-yl]sulfonyl]amino]-1-(phenylmethyl) propyl]-3-methyl-L-Valinamide. Mass spectral data : m/z = 758 (M+H).

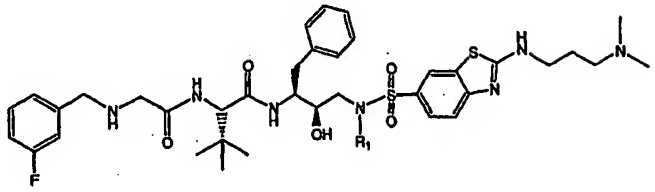
4.2 g of the previous intermediate, 1.2 g of Boc_2O and 0.77 mL of triethylamine were dissolved in 50 mL of dichloromethane. The reaction mixture was stirred overnight at room temperature and 1.2 g of Boc_2O were added. After 5h, the reaction mixture was successively washed with a solution of sodium carbonate in water, brine, dried over $MgSO_4$ and evaporated. The crude compound was purified on silica gel eluting with 2 to 5% methanol in dichloromethane, yielding 3.2 g (67%) of the desired intermediate **h-4** N'-[(1,1-dimethylethoxy)carbonyl]-N'-[(3-fluorophenyl)methyl]glycyl-N-[(1S,2R)-2-hydroxy-3-[(2-methylpropyl)[[2-(methylthio)benzothiazol-6-yl]sulfonyl] amino]-1-(phenylmethyl)propyl]-3-methyl-L-Valinamide. Mass spectral data : m/z = 858 (M+H).

3.2 g of intermediate **h-4** and 0.92 g of meta-chloroperoxybenzoic acid (mCPBA) were reacted in 100 mL of dichloromethane, at room temperature, during 1h30. The reaction mixture was then washed with a solution of sodium carbonate in water, dried over $MgSO_4$ and evaporated to yield 3.45 g (100%) of the desired intermediate **h-5** N'-[(1,1-dimethylethoxy)carbonyl]-N'-[(3-fluorophenyl)methyl]glycyl-N-[(1S,2R)-2-hydroxy-3-[(2-methylpropyl)[[2-(methylsulfinyl)benzothiazol-6-yl]sulfonyl]amino]-1-(phenylmethyl)propyl]-3-methyl-L-Valinamide. Mass spectral data : m/z = 874 (M+H).

0.5 g of intermediate **h-5** was reacted with 0.16 mL of N-(2-aminoethyl)pyrrolidine in 10 mL of acetonitrile, at 60°C, during 1h30. The reaction mixture was then evaporated and purified on silica gel eluting with 5 to 10% methanol in dichloromethane, yielding 0.24 g (46%) of the desired intermediate N'-[(1,1-dimethylethoxy)carbonyl]-N'-[(3-fluorophenyl)methyl]glycyl-N-[(1S,2R)-2-hydroxy-3-[(2-methylpropyl)[[2-[2-(pyrrolidin-1-yl)ethylamino]benzothiazol-6-yl]sulfonyl]amino]-1-(phenylmethyl)propyl]-3-methyl-L-Valinamide. Mass spectral data : m/z = 924 (M+H).

0.15 g of the previous intermediate was dissolved in 5 mL of HCl in isopropanol. The reaction mixture was stirred at room temperature during 2h, then evaporated. The crude compound was purified by preparative HPLC, yielding 60 mg of the desired final compound **85** N'-[(3-fluorophenyl)methyl]glycyl-N-[(1S,2R)-2-hydroxy-3-[(2-methylpropyl)[[2-[2-(pyrrolidin-1-yl)ethylamino]benzothiazol-6-yl]sulfonyl]amino]-1-(phenylmethyl)propyl]-3-methyl-L-Valinamide, bis-trifluoroacetate, obtained as a TFA salt. Mass spectral data : m/z = 824 (M+H).

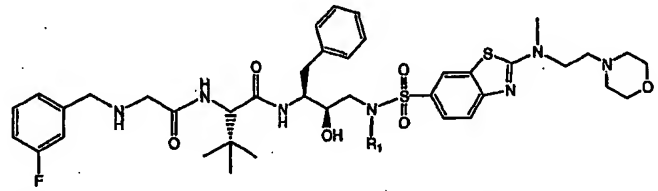
Example 16 : Preparation of the compound 86(R_1 = isobutyl)



0.5 g of intermediate **h-5** was reacted with 0.16 mL of 3-(dimethylamino)propylamine in 10 mL of acetonitrile, at 60°C, during 2h. The reaction mixture was then evaporated, yielding 0.54 g (100%) of the desired intermediate N'-[(1,1-dimethylethoxy)carbonyl]-N'-[(3-fluorophenyl)methyl]glycyl-N-[(1S,2R)-2-hydroxy-3-[[[2-[3-(dimethylamino)propylamino]benzothiazol-6-yl]sulfonyl](2-methyl propyl)amino]-1-(phenylmethyl)propyl]-3-methyl-L-Valinamide. Mass spectral data : m/z = 912 (M+H).

0.54 g of the previous intermediate was dissolved in 10 mL of HCl in isopropanol. The reaction mixture was stirred at room temperature during 2h, then evaporated. The crude compound was purified by preparative HPLC, yielding 83 mg of the desired final compound **86** N'-[(3-fluorophenyl)methyl]glycyl-N-[(1S,2R)-2-hydroxy-3-[[[2-[3-(dimethylamino)propylamino]benzothiazol-6-yl]sulfonyl](2-methylpropyl)amino]-1-(phenylmethyl)propyl]-3-methyl-L-Valinamide, bis-trifluoroacetate, obtained as a TFA salt. Mass spectral data : m/z = 812 (M+H).

Example 17 : Preparation of the compounds 87 (R_1 = isobutyl)

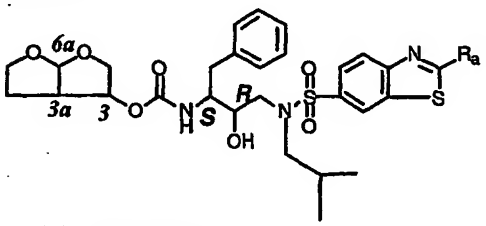


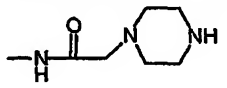
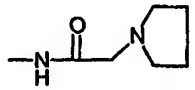
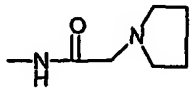
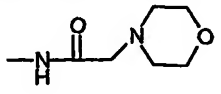
0.5 g of intermediate **h-5** was reacted with 0.18 mg of *N*-methyl, *N*-(2-morpholin-4-ylethyl)amine in 10 mL of acetonitrile, at 60°C, overnight. 0.9 g of *N*-methyl, *N*-(2-morpholin-4-ylethyl)amine was then added again to the reaction mixture, which was further stirred during two days. The reaction mixture was then evaporated and purified on silica gel eluting with 5% methanol in dichloromethane, yielding 0.6 g (100%) of the desired intermediate N'-[(1,1-dimethylethoxy)carbonyl]-N'-[(3-fluorophenyl) methyl]glycyl-N-[(1S,2R)-2-hydroxy-3-[[[2-[*N*-methyl,*N*-(2-morpholin-4-ylethyl) amino]benzothiazol-6-yl]sulfonyl](2-methylpropyl)amino]-1-(phenylmethyl)propyl]-3-methyl-L-Valinamide. Mass spectral data : m/z = 954 (M+H).

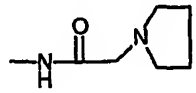
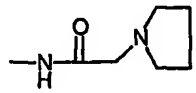
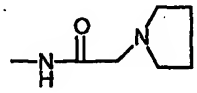
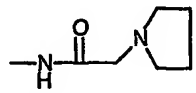
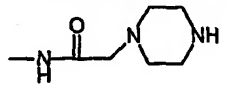
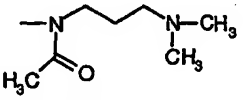
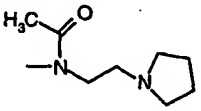
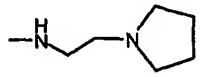
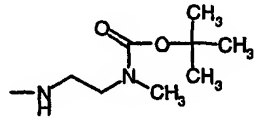
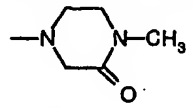
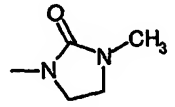
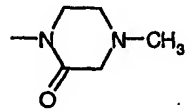
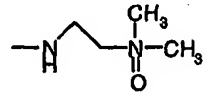
0.6 g of the previous intermediate was dissolved in 100 mL of HCl in isopropanol. The reaction mixture was stirred at room temperature during 2h, then evaporated and treated with a mixture of dichloromethane and a solution of sodium carbonate in water. The organic phase was then dried over $MgSO_4$ and evaporated. The crude compound was purified by preparative HPLC, yielding 424 mg (60%) of the desired final compound **87** N'-[(3-fluorophenyl)methyl]glycyl-N-[(1S,2R)-2-hydroxy-3-[[[2-[N-methyl,N-(2-morpholin-4-ylethyl)amino]benzothiazol-6-yl]sulfonyl](2-methylpropyl)amino]-1-(phenylmethyl)propyl]-3-methyl-L-Valinamide, bis-trifluoroacetate, obtained as a TFA salt. Mass spectral data : m/z = 854 (M+H).

The following tables list the compounds of formula (I) which were prepared following one of the above reaction schemes.

Table 1



Co. No.	Scheme	R_a	salt form / stereochemistry of bicyclic ring
1	A	-NH-CO-CH_3	free base / (3R,3aS,6aR) + (3S,3aR,6aS)
2	A	-NH-COO-C_2H_5	free base / (3R,3aS,6aR) + (3S,3aR,6aS)
3	D	-NH-CO-CH_2-N(CH_3)$_2$	free base / (3R,3aS,6aR) + (3S,3aR,6aS)
4	B	-NH-(CH_2)$_2$-N(CH_3)$_2$	free base / (3R,3aS,6aR) + (3S,3aR,6aS)
5	D		free base / (3R,3aS,6aR) + (3S,3aR,6aS)
6	D	-NH-CH_2-$COOCH_3$	free base / (3R,3aS,6aR) + (3S,3aR,6aS)
7	D		free base / (3R,3aS,6aR) + (3S,3aR,6aS)
8	D		HCl (1:1) / (3R,3aS,6aR) + (3S,3aR,6aS)
9	A	-N(CH_3)-$COCH_3$	free base / (3R,3aS,6aR) + (3S,3aR,6aS)
10	D		free base / (3R,3aS,6aR) + (3S,3aR,6aS)
11	D	-NH-CO-CH_2-N(CH_3)$_2$	free base / (3R,3aS,6aR)

Co. No.	Scheme	R_a	salt form / stereochemistry of bicyclic ring
12	D		free base / (3R,3aS,6aR)
13	D		fumarate (1:1) / (3R,3aS,6aR)
14	D		HCl (1:1) / (3R,3aS,6aR)
15	D		oxalate (1:1) / (3R,3aS,6aR)
16	C	$-NH-(CH_2)_2-N(CH_3)_2$	free base / (3R,3aS,6aR)
17	D		free base / (3R,3aS,6aR)
18	B		free base / (3R,3aS,6aR)
19	B		free base / (3R,3aS,6aR)
20	B		free base / (3R,3aS,6aR)
21	B		free base / (3R,3aS,6aR)
22	B	$-NH-(CH_2)_3-N(CH_3)_2$	free base / (3R,3aS,6aR)
23	B	$-NH-(CH_2)_2-NH(CH_3)$	free base / (3R,3aS,6aR)
24	B		free base / (3R,3aS,6aR)
25	B		free base / (3R,3aS,6aR)
26	B		free base / (3R,3aS,6aR)
27	C		free base / (3R,3aS,6aR)

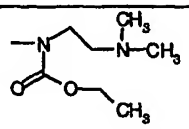
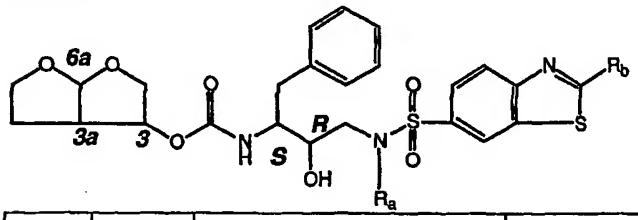
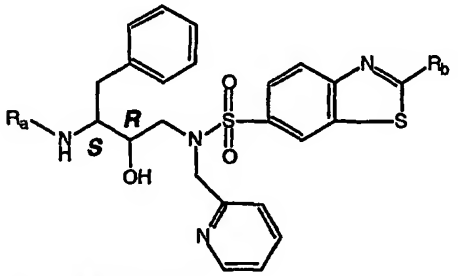
Co. No.	Scheme	R_a	salt form / stereochemistry of bicyclic ring
28	B		free base / (3R,3aS,6aR)

Table 2



Co. No.	Scheme	R_a	R_b	Salt / stereochemistry of bicyclic ring
29	A	$-(CH_2)_2$-NH-(2-pyridinyl)	$-NH-CO-CH_3$	free base / (3R,3aS,6aR) + (3S,3aR,6aS)

Table 3



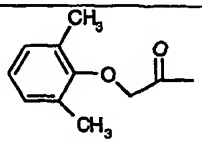
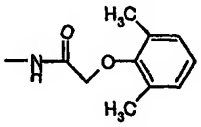
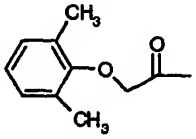
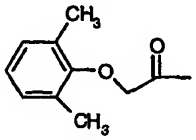
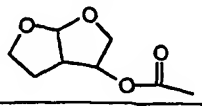
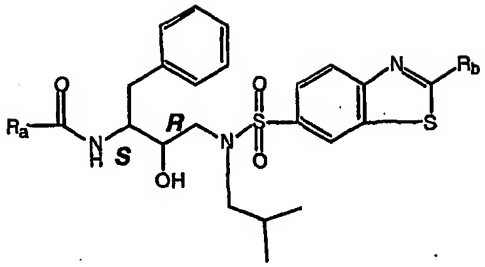
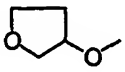
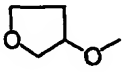
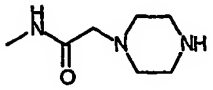
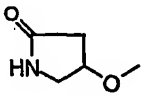
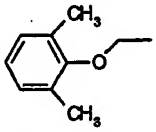
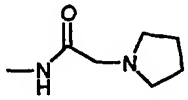
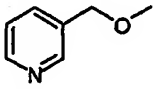
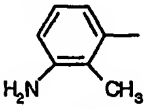
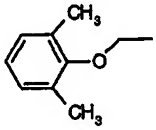
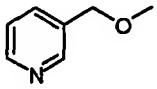
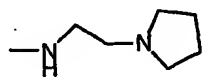
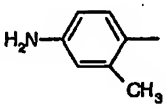
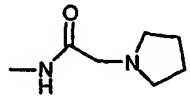
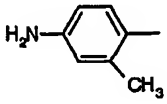
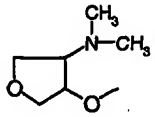
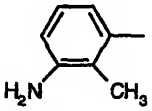
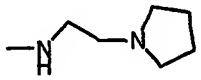
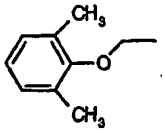
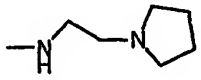
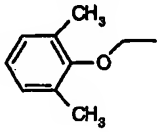
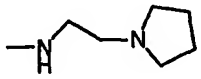
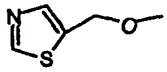
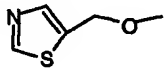
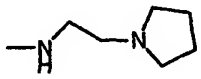
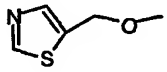
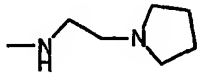
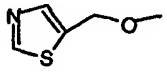
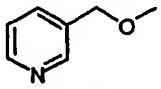
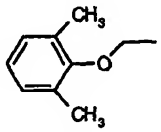
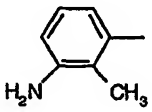
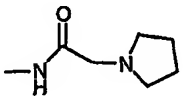
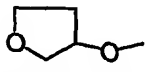
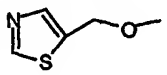
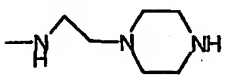
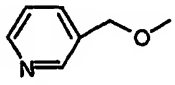
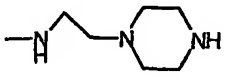
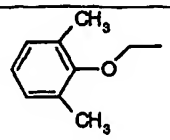
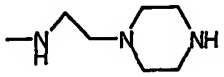
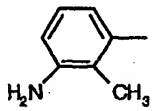
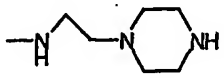
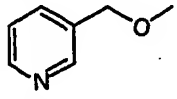
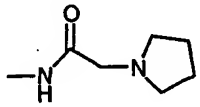
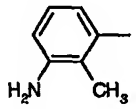
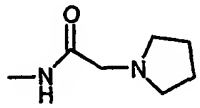
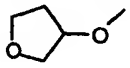
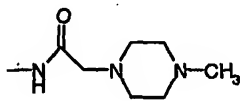
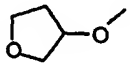
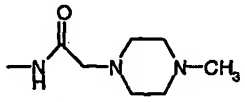
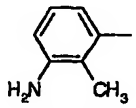
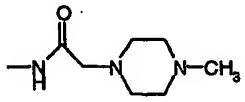
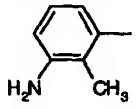
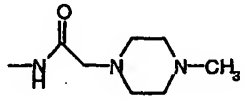
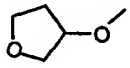
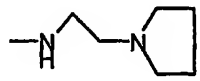
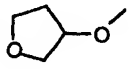
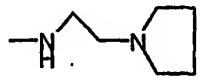
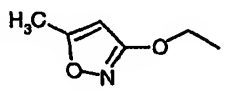
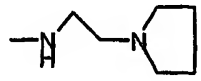
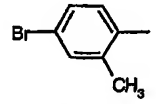
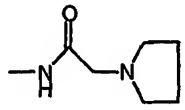
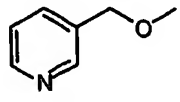
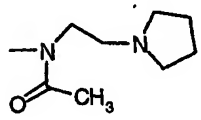
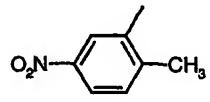
Co. No.	Scheme	R_a	R_b	Salt / stereochemistry in R_a group
30	D			free base / -
31	A		$-N(CH_3)-CO-CH_3$	free base / -
32	A		$-N(CH_3)-CO-CH_3$	trifluoroacetate (1:1) / -
33	A		$-N(CH_3)-CO-CH_3$	free base / (3R,3aS,6aR)+(3S,3aR,6aS)

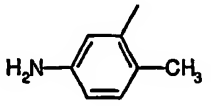
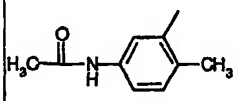
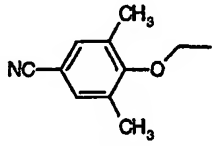
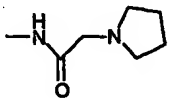
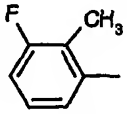
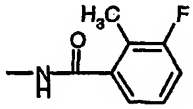
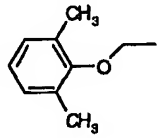
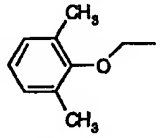
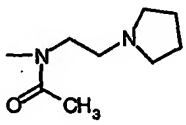
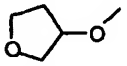
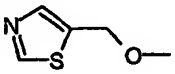
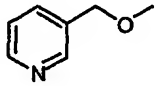
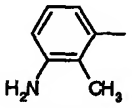
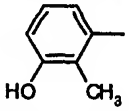
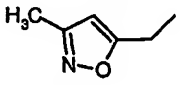
Table 4



Co. No.	Scheme	R_a	R_b	Salt / stereochemistry in R_a group
34	D		$-NH-CO-CH_2-N(CH_3)_2$	free base / 3S
35	D			free base / 3S
36	D		$-NH-CO-CH_2-N(CH_3)_2$	free base / 3S
37	E			free base / -
38	B		$-NH-(CH_2)_2-N(CH_3)_2$	free base / -
39	B		$-NH-(CH_2)_2-N(CH_3)_2$	free base / -
40	B		$-NH-(CH_2)_2-N(CH_3)_2$	free base / -
41	B			free base / -
42	D			free base / -
43	D		$-NH-CO-CH_2-N(CH_3)_2$	free base / -
44	B		$-NH-(CH_2)_2-N(CH_3)_2$	free base / ± *trans*

Co. No.	Scheme	R_a	R_b	Salt / stereochemistry in R_a group
45	B			free base / -
46	B			free base / -
47	B			trifluoroacetate (1:1) / -
48	B		$-NH-(CH_2)_2-N(CH_3)_2$	free base / -
49	B			free base / -
50	B			trifluoroacetate (1:1) / -
51	B		$-NH-(CH_2)_3-N(CH_3)_2$	free base / -
52	B		$-NH-(CH_2)_3-N(CH_3)_2$	free base / -
53	B		$-NH-(CH_2)_3-N(CH_3)_2$	free base / -
54	B		$-NH-(CH_2)_3-N(CH_3)_2$	free base / -
55	B	H		free base / -
56	B		$-NH-(CH_2)_2-N(CH_3)_2$	free base / 3S
57	B			free base / -
58	B			free base / -

Co. No.	Scheme	R_a	R_b	Salt / stereochemistry in R_a group
59	B			free base / -
60	B			free base / -
61	D			free base / -
62	D			free base / -
63	B			free base / 3S
64	B			Trifluoroacetate (1:1) / 3S
65	B			free base / -
66	B			Trifluoroacetate (1:1) / -
67	B			free base / 3S
68	B			Trifluoroacetate (1:1) / 3S
69	B			free base / -
70	E			free base / -
71	B			free base / -
72	A		-NH-CO-CH_3	free base / -

Co. No.	Scheme	R_a	R_b	Salt / stereochemistry in R_a group
73	A		-NH-CO-CH_3	free base / -
74	A		-NH-CO-CH_3	free base / -
75	E			free base / -
76	A			free base / -
77	A		-N(CH_3)-CO-CH_3	free base / -
78	B			free base / -
79	A		-N(CH_3)-CO-CH_3	free base / 3S
80	A		-N(CH_3)-CO-CH_3	free base / -
81	A		-N(CH_3)-CO-CH_3	free base / -
82	A		-N(CH_3)-CO-CH_3	free base / -
83	A		-N(CH_3)-CO-CH_3	free base / -
84	A		-NH-CO-CH_3	free base / -

Examples of compounds according to the invention are shown in Table 5

Table 5

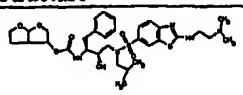
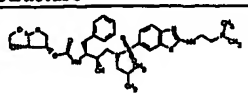
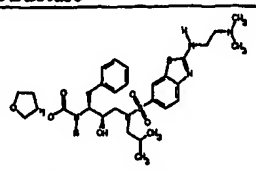
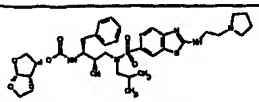
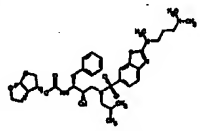
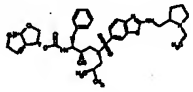
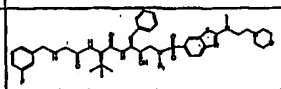
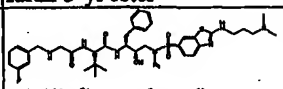
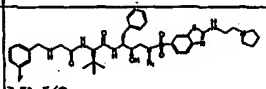
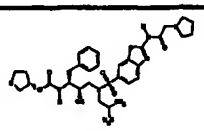
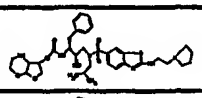
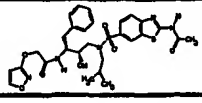
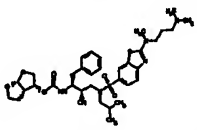
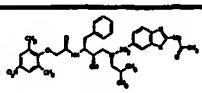
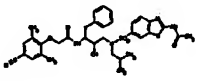
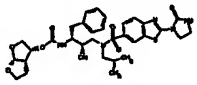
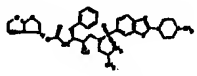
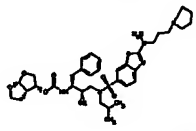
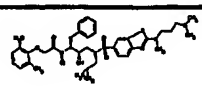
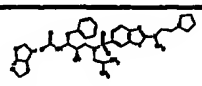
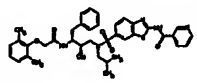
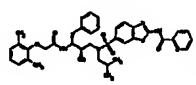
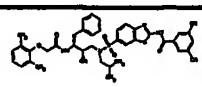
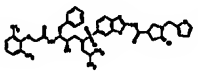
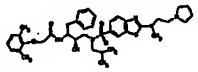
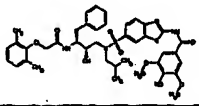
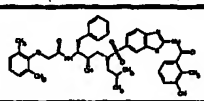
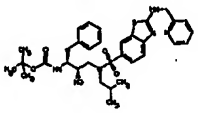
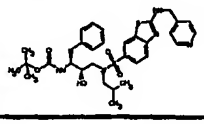
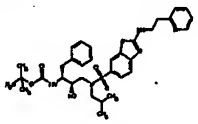
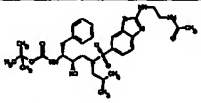
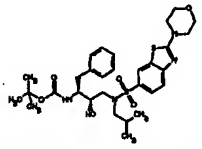
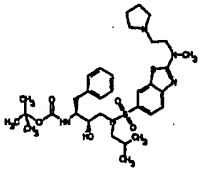
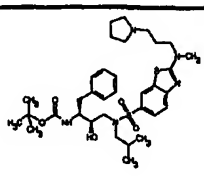
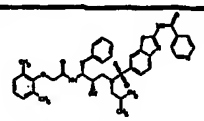
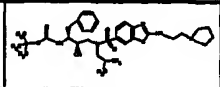
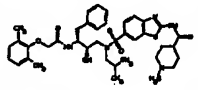
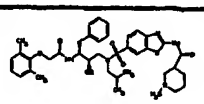
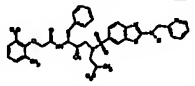
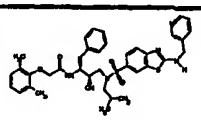
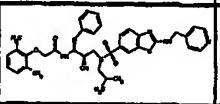
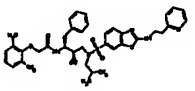
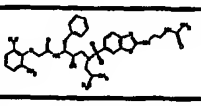
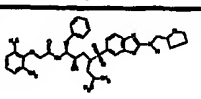
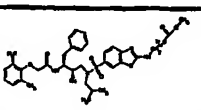
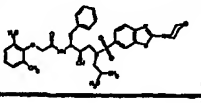
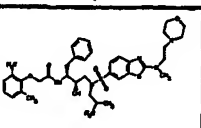
Co	Structure	Co	Structure	Co	Structure
04		16	 (1-Benzyl-3-{[2-(2-dimethylamino-ethylamino)-benzothiazole-6-sulfonyl]-isobutyl-amino}-2-hydroxy-propyl)-carbamic acid hexahydro-furo[2,3-b] furan-3-yl ester	90	 (1-Benzyl-3-{[2-(2-dimethylamino-ethylamino)-benzothiazole-6-sulfonyl]-isobutyl-amino}-2-hydroxy-propyl)-carbamic acid tetrahydro-furan-3-yl ester
20	 1-Benzyl-2-hydroxy-3-{isobutyl-[2-(2-pyrrolidin-1-yl-ethylamino)-benzothiazole-6-sulfonyl]-amino}-propyl)-carbamic acid hexahydro-furo[2,3-b] furan-3-yl ester	88	 [1-Benzyl-3-({2-[(3-dimethylamino-propyl)-methyl-amino]-benzothiazole-6-sulfonyl}-isobutyl-amino)-2-hydroxy-propyl]-carbamic acid hexahydro-furo[2,3-b] furan-3-yl ester	93	 [1-Benzyl-3-({2-[(1-ethyl-pyrrolidin-2-ylmethyl)-amino]-benzothiazole-6-sulfonyl}-isobutyl-amino)-2-hydroxy-propyl]-carbamic acid hexahydro-furo[2,3-b] furan-3-yl ester
87	 N'-[(3-fluorophenyl)methyl] glycyl-N-[(1S,2R)-2-hydroxy-3-[[[2-[N-methyl,N-(2-morpholin-4-ylethyl)amino]benzothiazol-6-yl]sulfonyl](2-methylpropyl)amino]-1-(phenylmethyl)propyl]-3-methyl-L-Valinamide, bis-trifluoroacetate	86	 N'-[(3-fluorophenyl) methyl]glycyl-N-[(1S,2R)-2-hydroxy-3-[[[2-[3-(dimethylamino)propylamino]benzothiazol-6-yl]sulfonyl](2-methylpropyl)amino]-1-(phenylmethyl)propyl]-3-methyl-L-Valinamide, bis-trifluoroacetate.	85	 N'-[(3-fluorophenyl)methyl]glycyl-N-[(1S,2R)-2-hydroxy-3-[(2-methylpropyl)[[2-[2-(pyrrolidin-1-yl)ethylamino]benzothiazol-6-yl]sulfonyl]amino]-1-(phenylmethyl)propyl]-3-methyl-L-Valinamide, bis-trifluoroacetate

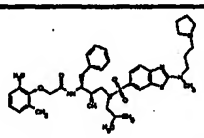
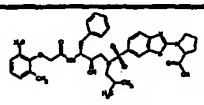
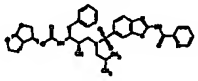
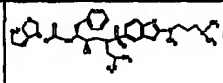
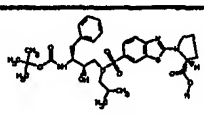
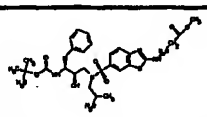
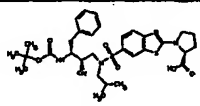
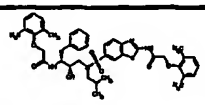
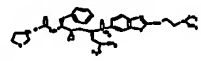
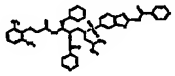
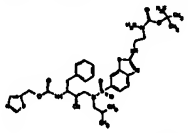
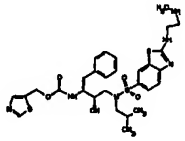
Table 6

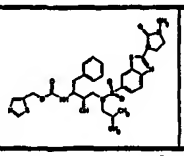
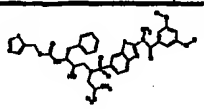
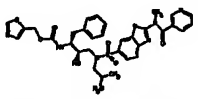
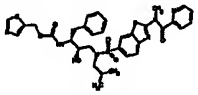
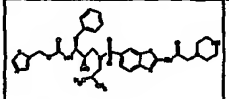
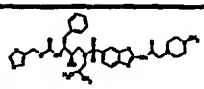
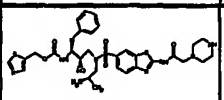
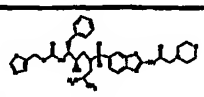
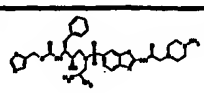
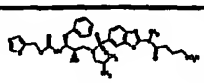
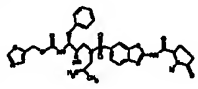
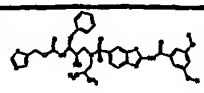
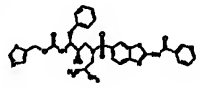
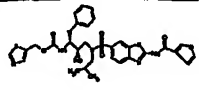
The following compounds were also prepared. The compounds were evaluated according to the methods described infra. Column 3 displays the results as pEC50 against wild type virus (IIIB). Column 4 displays the results as pEC50 against wild virus strain F (R13025). Column 5 displays the results as pEC50 against wild virus strain S (R13080).

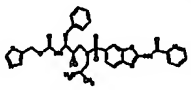
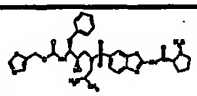
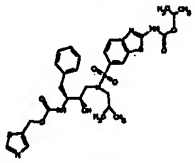
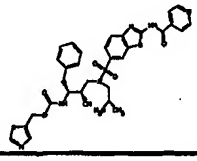
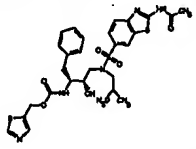
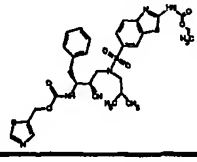
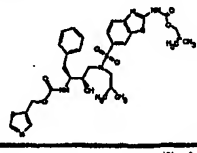
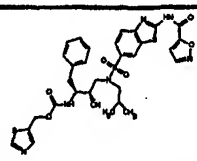
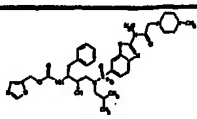
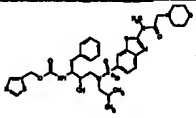
Compound number	Structure	HIV-AVE-MT4-MTT-IIIB-2-002 pEC50	HIV-AVE-MT4-MTT-R13025-2-002 pEC50	HIV-AVE-MT4-MTT-R13080-2-002 pEC50
100		8.88	7.36	7.15
101		6.62		
102		7.92	6.88	6.02
103		7.7	6.76	6.28
104		7.18		
105		7.33	7.25	6.32
106		7.96	7.26	6.66
107		8.7	6.8	6.18
108		7.61	6.54	6.09
109		5.68	5.38	
110		8.09	6.17	5.81
111		7.61	6.63	6.18
112		8	6.91	6.82
113		8.29	7.61	7.36

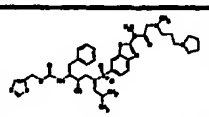
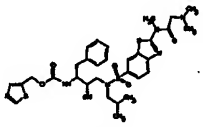
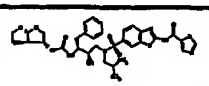
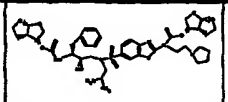
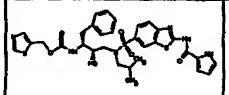
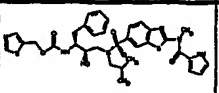
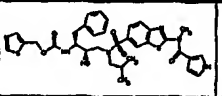
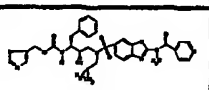
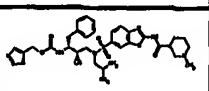
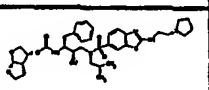
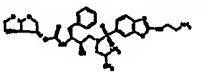
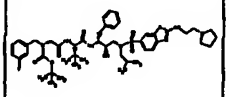
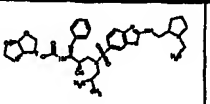
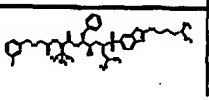
Compound number	Structure	HIV-AVE-MT4-MTT-IIIB-2-002 pEC50	HIV-AVE-MT4-MTT-R13025-2-002 pEC50	HIV-AVE-MT4-MTT-R13080-2-002 pEC50
114		7.69	7.47	6.85
115		6.12	5.21	5
116		7.5	7.49	7.36
117		7.32	7.45	6.72
118		6.52		
119		6.48		
120		6.5		
121		7.68	5.55	5
122		5.92		
123		5.8		
124		5.7		

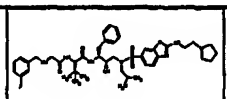
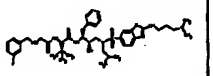
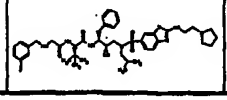
Compound number	Structure	HIV-AVE-MT4-MTT-IIIB-2-002 pEC50	HIV-AVE-MT4-MTT-R13025-2-002 pEC50	HIV-AVE-MT4-MTT-R13080-2-002 pEC50
125		8.2	7.57	6.84
126		7.31	5.5	5
127		7.78	7.5	6.87
128		8.23	7.72	7.25
129		7.2		
130		7.23		
131		7.33	6.08	5.98
132		7.19		
133		7.67	7.47	6.8
134		7.21		
135		7.18		
136		6.14		
137		5.77		

Compound number	Structure	HIV-AVE-MT4-MTT-IIIB-2-002 pEC50	HIV-AVE-MT4-MTT-R13025-2-002 pEC50	HIV-AVE-MT4-MTT-R13080-2-002 pEC50
138		5.84		
139		5.68	5.51	5
140		8.34	8.12	
141		7.83	6.49	6.02
142		5.25		
143		7.13	5	5
144		0		
145		7.9	7.4	6.84
146		8.02	6.52	6
147		6.47		
148		6.43	6.51	6.56
149		7.29		
150		7.37	6.79	6.18

Compound number	Structure	HIV-AVE-MT4-MTT-IIIB-2-002 pEC50	HIV-AVE-MT4-MTT-R13025-2-002 pEC50	HIV-AVE-MT4-MTT-R13080-2-002 pEC50
151		6.97	6.09	5.57
152		7.48	6.25	5.76
153		8.13	7.34	6.47
154		8.26	7.42	6.43
155		7.37	7.61	7.49
156		8.14	8.27	7.56
157		7.54	7.5	6.85
158		8.48	8.1	7.52
159		8.1	7.78	7.46
160		7.29	6.32	5.61
161		8.04	7.76	7.47
162		7.69	7.33	6.8
163		7.94	7.31	6.67
164		8.15	7.47	6.8

Compound number	Structure	HIV-AVE-MT4-MTT-IIIB-2-002 pEC50	HIV-AVE-MT4-MTT-R13025-2-002 pEC50	HIV-AVE-MT4-MTT-R13080-2-002 pEC50
165		7.35	6.91	6.2
166		8.2	7.66	7.13
167		8.31	7.51	6.85
168		7.61	7.5	6.87
169		8.07	8.17	7.45
170		8.12	7.76	6.79
171		7.29	6.73	6.07
172		7.37	6.61	6.09
173		8.25	7.52	6.81
174		8.04	6.88	6.18

Compound number	Structure	HIV-AVE-MT4-MTT-IIIB-2-002 pEC50	HIV-AVE-MT4-MTT-R13025-2-002 pEC50	HIV-AVE-MT4-MTT-R13080-2-002 pEC50
175		7.3	6.03	5.5
176		8.39	7.2	6.65
177		7.43	8.12	7.31
178		7.76	7.97	7.47
179		8.05	7.24	7.32
180		6.81	6.05	5
181		7.48	6.28	5.74
182		8.32	7.44	6.77
183		8.45	8.77	8.15
184		7.76	8.35	7.57
185		7.34	7.48	7.46
85		7.24		
186		8.21	8.18	7.54
86				

Compound number	Structure	HIV-AVE-MT4-MTT-IIIB-2-002 pEC50	HIV-AVE-MT4-MTT-R13025-2-002 pEC50	HIV-AVE-MT4-MTT-R13080-2-002 pEC50
187				
188		6.7	7.03	6.88
189		7.35	6.99	6.86

Antiviral analyses:

The compounds of the present invention were examined for anti-viral activity in a cellular assay. The assay demonstrated that these compounds exhibited potent anti-HIV activity against a wild type laboratory HIV strain (HIV-1 strain LAI). The cellular assay was performed according to the following procedure.

Cellular Assay Experimental Method:

HIV- or mock-infected MT4 cells were incubated for five days in the presence of various concentrations of the inhibitor. At the end of the incubation period, all HIV-infected cells have been killed by the replicating virus in the control cultures in the absence of any inhibitor. Cell viability is measured by measuring the concentration of MTT, a yellow, water soluble tetrazolium dye that is converted to a purple, water insoluble formazan in the mitochondria of living cells only. Upon solubilization of the resulting formazan crystals with isopropanol, the absorbance of the solution is monitored at 540nm. The values correlate directly to the number of living cells remaining in the culture at the completion of the five day incubation. The inhibitory activity of the compound was monitored on the virus-infected cells and was expressed as EC_{50} and EC_{90}. These values represent the amount of the compound required to protect 50% and 90%, respectively, of the cells from the cytopathogenic effect of the virus. The toxicity of the compound was measured on the mock-infected cells and was expressed as CC_{50}, which represents the concentration of compound required to inhibit the growth of the cells by 50%. The selectivity index (SI) (ratio CC_{50}/EC_{50}) is an indication of the selectivity of the anti-HIV activity of the inhibitor.

The compounds 1-4, 7, 9-19, 21, 24-26, 28, 33-35, 37-43, 45, 46, 49, 50, 56, 61-64, 66, 68, 70, 71, 75, 79-83 and 88-93 all have an EC_{50} value against HIV-1 strain LAI of less

than 50 nM. The SI for these compounds ranges between about 400 up to more than 47000.

The compounds 5, 6, 20, 22, 23, 29, 36, 44, 47, 48, 51-55, 58, 59, 69, 72-74, 76-78 and 84 all had an EC_{50} value against HIV-1 strain LAI between 50 nM and 500 nM. The SI for these compounds ranges between about 26 up to more than 1900.

The compounds 27, 30, 31, 57 and 60 have an EC_{50} against HIV-1 strain LAI of more than 500 nM. The SI for these compounds ranges between more than 13 up to more than 183.

Antiviral spectrum:

Because of the increasing emergence of drug resistant HIV strains, the present compounds were tested for their potency against clinically isolated HIV strains harboring several mutations. These mutations are associated with resistance to protease inhibitors and result in viruses that show various degrees of phenotypic cross-resistance to the currently commercially available drugs such as for instance saquinavir, ritonavir, nelfinavir, indinavir and amprenavir.

Results:

As a measure of the broad spectrum activity of the present compounds, the fold resistance (FR) defined as FR = EC_{50}(mutant strain)/EC_{50}(HIV-1 strain LAI). Table 7 shows the results of the antiviral testing in terms of fold resistance. As can be seen in this table, the present compounds are effective in inhibiting a broad range of mutant strains.

Table 7

Co	STRAIN																				
	LAI	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R	S	T
1	1	0.4	0.3	0.7	0.7	0.6	0.8	0.3	0.9	0.8	0.5	0.4	0.2	0.5	1.0	0.4	0.2	0.8	0.7	1.0	5.1
2	1	0.3	0.2	0.2	0.3	0.4	1.1	0.2	1.0	0.7	0.4	0.2	0.2	0.3	1.1	0.8	0.2	0.3	0.3	1.7	29.6
3	1	0.4	0.4	0.4	0.8	0.4	1.1	0.4	1.0	0.8	0.4	0.4	0.3	0.4	2.3	1.0	0.4	0.5	0.5	1.8	34.2
4	1	-	-	-	-	-	2.2	-	1.9	1.2	0.5	-	-	-	-	0.5	-	-	-	2.9	48.8
5	1	-	-	-	-	-	0.5	-	0.6	0.6	0.3	-	-	-	-	0.4	-	-	-	0.6	2.6
6	1	-	-	-	-	-	24.0	-	7.7	5.3	5.6	-	-	-	-	4.7	-	-	-	30.7	104.3
7	1	0.2	0.3	0.5	0.5	0.3	0.5	0.2	0.5	0.5	0.4	0.3	0.1	0.1	0.5	0.4	0.1	0.4	0.4	2.0	12.4
9	1	1.5	1.5	1.6	5.7	2.3	13.0	1.5	6.7	2.3	6.2	1.0	0.7	0.5	1.5	3.7	0.2	1.8	1.2	29.3	550.9
10	1	0.4	0.4	0.6	0.5	0.4	0.5	0.5	0.4	0.4	0.3	0.3	0.2	0.3	0.0	0.4	0.3	0.3	0.3	0.5	4.9
11	1	0.3	0.4	0.5	0.3	-	0.7	0.5	0.9	0.5	0.4	0.4	0.3	0.4	1.6	0.7	0.3	0.0	0.5	1.1	7.3
12	1	0.3	0.4	0.3	0.4	0.4	0.4	0.2	0.4	0.4	0.3	0.2	0.1	0.2	0.4	0.4	0.1	0.4	0.4	0.8	5.9
13	1	0.2	0.2	0.2	0.2	0.2	0.6	0.2	0.6	0.3	0.2	0.2	0.1	0.2	1.0	0.3	0.2	0.4	0.2	1.0	5.8
14	1	0.2	0.2	0.2	0.2	0.3	0.4	0.2	0.5	0.4	0.3	0.2	0.1	0.2	0.9	0.3	0.2	0.3	0.2	0.7	5.9
15	1	0.3	0.2	0.3	0.3	0.3	0.5	0.3	0.5	0.3	0.3	0.3	0.1	0.2	0.4	0.2	0.1	0.2	0.2	0.8	7.2
16	1	0.2	0.3	0.2	0.2	0.3	0.4	0.2	0.3	0.3	0.3	0.2	0.1	0.2	0.4	0.3	0.1	0.2	0.2	1.6	6.6
17	1	-	-	-	-	-	0.3	-	0.8	0.7	0.2	-	-	-	-	0.3	-	-	-	0.6	1.0
18	1	-	-	-	-	-	1.0	-	1.0	0.9	0.9	-	-	-	-	0.9	-	-	-	1.0	5.4
19	1	-	-	-	-	-	2.4	-	2.1	1.1	0.6	-	-	-	-	0.5	-	-	-	2.2	10.5
20	1	-	-	-	-	-	0.5	-	0.5	0.4	0.2	-	-	-	-	0.2	-	-	-	0.5	2.6
21	1	-	-	-	-	-	16.6	-	4.8	3.7	3.3	-	-	-	-	3.4	-	-	-	38.6	380.0
22	1	-	-	-	-	-	0.3	-	0.4	0.6	0.4	-	-	-	-	0.4	-	-	-	1.4	6.0
23	1	-	-	-	-	-	1.1	-	1.2	1.0	1.0	-	-	-	-	0.9	-	-	-	1.1	1.2
24	1	-	-	-	-	-	16.6	-	4.7	1.1	4.5	-	-	-	-	1.6	-	-	-	24.1	174.9

Co	STRAIN																				
	LAI	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R	S	T
25	1	-	-	-	-	-	26.0	-	4.7	3.5	6.0	-	-	-	-	5.6	-	-	-	42.5	619.8
26	1	-	-	-	-	-	29.6	-	20.3	6.6	9.2	-	-	-	-	10.6	-	-	-	34.1	345.6
27	1	-	-	-	-	-	1.4	-	1.2	1.3	0.7	-	-	-	-	0.6	-	-	-	5.1	5.4
28	1	-	-	-	-	-	2.3	-	1.8	1.4	0.7	-	-	-	-	0.8	-	-	-	4.4	12.7
30	1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
31	1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
33	1	-	-	-	-	-	7.6	-	6.8	7.1	5.9	-	-	-	-	3.4	-	-	-	467.3	467.3
34	1	5.0	5.9	5.5	6.6	4.5	61.9	3.2	11.4	5.6	5.8	1.3	1.2	1.2	4.0	5.0	0.9	4.0	1.1	99.6	802.7
35	1	0.5	0.9	0.6	0.5	0.9	2.1	0.5	0.8	0.8	0.8	0.4	0.2	0.6	1.1	0.3	0.2	0.9	0.9	4.3	22.2
36	1	-	-	-	-	-	0.2	-	0.6	0.5	0.2	-	-	-	-	0.2	-	-	-	0.2	0.2
37	1	6.1	1.9	3.8	1.4	1.6	6.1	1.3	4.1	6.8	5.0	0.5	2.1	5.0	1.4	7.3	0.3	3.8	1.5	10.0	185.8
38	1	-	-	-	-	-	12.4	-	2.0	1.1	3.9	-	-	-	-	1.2	-	-	-	11.9	230.4
39	1	-	-	-	-	-	19.7	-	2.3	2.4	2.2	-	-	-	-	1.7	-	-	-	16.5	249.9
40	1	-	-	-	-	-	7.2	-	2.1	6.4	2.7	-	-	-	-	3.2	-	-	-	12.8	87.8
41	1	-	-	-	-	-	44.4	-	2.3	2.5	5.6	-	-	-	-	2.0	-	-	-	37.6	252.5
42	1	0.9	0.4	0.9	0.5	0.3	1.2	0.7	0.9	1.9	1.6	0.5	0.6	0.7	1.0	2.1	0.2	1.1	1.0	2.4	24.5
43	1	1.1	0.9	1.1	0.9	0.7	1.1	0.6	1.3	1.5	3.4	0.4	1.0	1.2	1.2	2.4	0.2	1.1	1.0	3.0	31.4
44	1	-	-	-	-	-	80.2	-	29.4	7.5	29.5	-	-	-	-	11.2	-	-	-	89.3	89.3
45	1	-	-	-	-	-	17.3	-	1.2	4.0	1.1	-	-	-	-	1.3	-	-	-	19.9	103.0
46	1	-	-	-	-	-	4.7	-	1.3	3.3	2.8	-	-	-	-	3.2	-	-	-	7.1	44.4
47	1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
48	1	-	-	-	-	-	9.4	-	2.5	2.5	6.5	-	-	-	-	4.3	-	-	-	13.8	175.0
49	1	-	-	-	-	-	12.8	-	3.6	2.9	5.5	-	-	-	-	3.9	-	-	-	17.8	114.0
50	1	-	-	-	-	-	8.6	-	1.4	1.7	7.0	-	-	-	-	3.5	-	-	-	27.9	165.5
51	1	-	-	-	-	-	2.9	-	1.8	2.6	0.9	-	-	-	-	0.6	-	-	-	2.1	51.8

Co	STRAIN																				
	LAI	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R	S	T
52	1	-	-	-	-	-	10.2	-	1.8	1.3	2.7	-	-	-	-	1.6	-	-	-	20.3	124.5
53	1	-	-	-	-	-	2.1	-	0.6	1.3	1.4	-	-	-	-	1.6	-	-	-	3.8	49.8
54	1	-	-	-	-	-	3.6	-	0.6	0.9	0.4	-	-	-	-	0.4	-	-	-	1.8	1.4
55	1	-	-	-	-	-	26.2	-	10.0	9.1	26.2	-	-	-	-	26.2	-	-	-	26.2	26.2
56	1	-	-	-	-	-	33.1	-	4.6	3.2	2.8	-	-	-	-	2.1	-	-	-	67.1	509.6
57	1	-	-	-	-	-	1.3	-	1.6	1.3	1.3	-	-	-	-	1.3	-	-	-	1.6	9.0
58	1	-	-	-	-	-	2.1	-	1.6	0.7	2.0	-	-	-	-	1.7	-	-	-	4.4	27.0
59	1	-	-	-	-	-	2.3	-	1.2	1.2	1.7	-	-	-	-	2.0	-	-	-	4.7	22.2
60	1	-	-	-	-	-	1.2	-	1.3	1.3	0.6	-	-	-	-	1.1	-	-	-	1.4	4.1
61	1	-	-	-	-	-	32.7	-	5.2	4.8	10.6	-	-	-	-	7.1	-	-	-	80.0	1090.0
62	1	-	-	-	-	-	14.5	-	3.2	2.8	2.4	-	-	-	-	2.7	-	-	-	16.1	277.9
63	1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
64	1	0.7	0.7	0.6	0.6	0.7	4.6	0.6	0.9	1.3	1.0	0.7	0.2	0.7	0.9	0.8	0.2	2.3	0.6	17.0	165.5
66	1	-	-	-	-	-	4.0	-	0.9	1.0	1.2	-	-	-	-	1.0	-	-	-	5.6	87.9
68	1	-	-	-	-	-	65.2	-	7.3	2.4	3.9	-	-	-	-	3.5	-	-	-	180.7	775.2
69	1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
70	1	-	-	-	-	-	4.7	-	3.1	3.7	3.3	-	-	-	-	3.2	-	-	-	10.4	145.1
71	1	-	-	-	-	-	29.6	-	2.7	2.2	7.0	-	-	-	-	5.0	-	-	-	79.6	321.5
72	1	-	-	-	-	-	67.0	-	24.9	26.2	11.4	-	-	-	-	24.4	-	-	-	118.0	641.1
73	1	-	-	-	-	-	43.1	-	9.8	12.1	14.1	-	-	-	-	20.7	-	-	-	966.6	966.6
74	1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
75	1	-	-	-	-	-	16.3	-	3.6	7.4	19.4	-	-	-	-	18.7	-	-	-	19.0	93.6
76	1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
77	1	-	-	-	-	-	8.9	-	2.2	8.3	11.0	-	-	-	-	11.7	-	-	-	11.6	144.7

Co	STRAIN																				
	LAI	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R	S	T
78	1	-	-	-	-	-	4.8	-	2.6	3.9	2.9	-	-	-	-	8.9	-	-	-	12.1	60.5
79	1	-	-	-	-	-	113.0	-	12.1	3.9	9.8	-	-	-	-	7.4	-	-	-	313.0	893.1
80	1	-	-	-	-	-	17.4	-	5.7	3.9	17.6	-	-	-	-	8.1	-	-	-	26.6	457.6
81	1	-	-	-	-	-	106.8	-	5.6	6.1	29.6	-	-	-	-	20.4	-	-	-	121.0	387.6
82	1	-	-	-	-	-	13.8	-	5.0	4.4	5.5	-	-	-	-	8.0	-	-	-	17.9	214.1
83	1	-	-	-	-	-	106.6	-	4.6	7.4	8.4	-	-	-	-	1.5	-	-	-	132.1	438.6
84	1	-	-	-	-	-	54.3	-	11.7	13.0	19.6	-	-	-	-	6.1	-	-	-	195.4	195.4
88	1						8.7													26.3	
89	1						21.9													64.6	
90	1						28.8													128.8	
91	1						64.6													323.6	
92	1						31.6													104.7	
93	1						1.1													4.68	

The codes used for the strains are as follows

Strain	Resistance associated mutations
A	L10I, K20R, M36I, I54V, A71V, V82T, I84V
B	L10I, K20R, L24I, M36I, I54V, L63P, A71V, V82T, I84V
C	L10I, K20R, M36I, M46I, I54V, L63P, A71V, V82T, L90M
D	L10I, M36I, I54V, L63P, A71V, G73S, I84V, L90M
E	L10I, K20R, L24I, M36I, M46I, I54V, L63P, A71V, G73S, V82T, I84V, L90M
F	L10I, M46I, L63P, A71V, I84V
G	L10I, L24I, M36V, M46I, I54V, L63P, A71V, V82T, I84V
H	L10I, K20R, M36I, L63P, A71V, G73S, V77I, I84V, L90M
I	L10I, K20M, I54V, L63P, A71V, I84V, L90M
J	L10I, M36I, M46I, L63P, A71V, V77I, I84V, N88D, L90M
K	L10I, M36I, I54V, L63P, A71V, V82T, L90M

Strain	Resistance associated mutations
L	L10I, L24I, G48V, I54V, V77I, V82T, L90M
M	L10I, L24I, M36I, I54V, L63P, V82T, L90M
N	L10I, M46I, I54V, L63P, A71V, V82A, L90M
O	L10I, L24I, M36I, I54V, L63P, A71V, I84V
P	L10I, D30N, L63P, V77I, N88D
Q	L10I, K20R, I54L, L63P, A71V, G73S, L90M
R	L10I, M46I, I54V, L63P, A71T, V77I, V82A, L90M
S	L10F, M46I, L63P, A71V, I84V
T	V32I, M36I, M46I, I47V, I50V, L63P, L90M
U	L10F, M46I, I47V, L63P, A71V, I84V

Biovailability:

The bioavailability of the present compounds was measured in rats. The compounds were administered orally or intra peritoneal. Animals were sacrificed at different time points after administration, whole blood was collected and serum prepared by standard methods. Concentration of the compound in serum was determined by titrating the anti-HIV activity present in the sample according to the procedure described above. Serum concentrations were also measured by HPLC-MS.

Protein Binding analyses:

Human serum proteins like albumin (HSA) or alpha-1 acid glycoprotein (AAG) are known to bind many drugs, resulting in a possible decrease in the effectiveness of those compounds. In order to determine whether the present compounds would be adversely effected by this binding, the anti-HIV activity of the compounds was measured in the

presence of human serum, thus evaluating the effect of the binding of the protease inhibitors to those proteins.

Pharmacokinetic data

The pharmacokinetic properties of compounds 20, 88 and 90 were tested on rats and dogs. The compounds were evaluated in Whistar rats, source Iffa Credo, weighing approximately 350 g. Before dosing the animals were fasted overnight (approximately 12 h fasting period). The compounds were dissolved in DMSO. The results represented in the table concern the results from the oral dosing of the compounds. Blood was sampled at 30 min, 1h, 2h, 3h, no pre-dose sample was taken. The amount of the compound in the biological sample was determined using LC-MS. In the table below "or" means oral dosing, "mpk" means mg per kilogram.

The results are illustrated in Table 8.

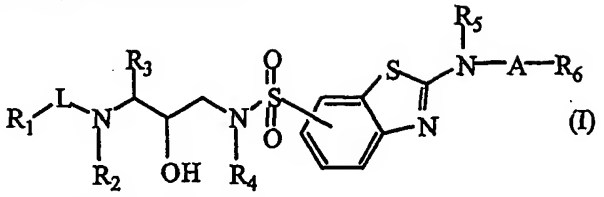
Table 8

Compound	C_{max} (ng/ml) (or, rat,10mpk, DMSO)	C_{3hours} (ng/ml) (or, rat,10mpk, DMSO)	C_{max} (ng/ml) (or, dog, 10mpk, DMSO)
20	1425	401	713
88	254	225	379(PEG)
90	893	684	550

A high plasma level can be observed for these compounds and more specifically for the compound such as compound **20**, which is due to the good solubility of said compounds in water.

CLAIMS

1. A compound having the formula (I)

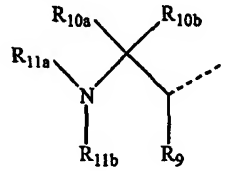


(I)

and *N*-oxides, salts, stereoisomeric forms, racemic mixtures, prodrugs, esters and metabolites thereof, wherein

R_1 and R_8 are, each independently, hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, arylC_{1-6}alkyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkylC_{1-6}alkyl, aryl, Het^1, Het^1C_{1-6}alkyl, Het^2, Het^2C_{1-6}alkyl;

R_1 may also be a radical of formula



(II)

wherein

R_9 , R_{10a} and R_{10b} are, each independently, hydrogen, C_{1-4}alkyloxycarbonyl, carboxyl, aminocarbonyl, mono- or di(C_{1-4}alkyl)aminocarbonyl, C_{3-7}cycloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl or C_{1-4}alkyl optionally substituted with aryl, Het^1, Het^2, C_{3-7}cycloalkyl, C_{1-4}alkyloxycarbonyl, carboxyl, aminocarbonyl, mono- or di(C_{1-4}alkyl)aminocarbonyl, aminosulfonyl, C_{1-4}alkyl$S(O)_t$, hydroxy, cyano, halogen or amino optionally mono- or disubstituted where the substituents are selected from C_{1-4}alkyl, aryl, arylC_{1-4}alkyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkylC_{1-4}alkyl, Het^1, Het^2, Het^1C_{1-4}alkyl and Het^2C_{1-4}alkyl; whereby R_9, R_{10a} and the carbon atoms to which they are attached may also form a C_{3-7}cycloalkyl radical; when L is -O-C_{1-6}alkanediyl-C(=O)- or -NR_8-C_{1-6}alkanediyl-C(=O)-, then R9 may also be oxo;

R_{11a} is hydrogen, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-7}cycloalkyl, aryl, arylC_{1-4}alkyl, aminocarbonyl optionally mono- or disubstituted, aminoC_{1-4}alkyl-carbonyloxy optionally mono- or disubstituted, C_{1-4}alkyloxycarbonyl, aryloxycarbonyl, Het^1oxycarbonyl, Het^2oxycarbonyl, aryloxycarbonyl-C_{1-4}alkyl, arylC_{1-4}alkyloxycarbonyl, C_{1-4}alkylcarbonyl, C_{3-7}cycloalkylcarbonyl, C_{3-7}cycloalkylC_{1-4}alkyloxycarbonyl, C_{3-7}cycloalkyl-carbonyloxy, carboxylC_{1-4}alkylcarbonyloxy, C_{1-4}alkylcarbonyloxy,

arylC$_{1-4}$alkylcarbonyloxy, arylcarbonyloxy, aryloxycarbonyloxy, Het^{1}carbonyl, Het^{1}carbonyloxy, Het^{1}C$_{1-4}$alkyloxycarbonyl, Het^{2}carbonyloxy, Het^{2}C$_{1-4}$alkylcarbonyloxy, Het^{2}C$_{1-4}$alkyloxycarbonyloxy or C$_{1-4}$alkyl optionally substituted with aryl, aryloxy, Het^2 , halogen or hydroxy; wherein the substituents on the amino groups are each independently selected from C$_{1-4}$alkyl, aryl, arylC$_{1-4}$alkyl, C$_{3-7}$cycloalkyl, C$_{3-7}$cycloalkylC$_{1-4}$alkyl, Het^1, Het^2, Het^{1}C$_{1-4}$alkyl and Het^{2}C$_{1-4}$alkyl;

R_{11b} is hydrogen, C$_{3-7}$cycloalkyl, C$_{2-6}$alkenyl, C$_{2-6}$alkynyl, aryl, C$_{1-6}$alkyloxycarbonyl, Het^1, Het^2 or C$_{1-4}$alkyl optionally substituted with halogen, hydroxy, C$_{1-4}$alkylS(=O)$_t$, aryl, C$_{3-7}$cycloalkyl, Het^1, Het^2, amino optionally mono- or disubstituted where the substituents are selected from C$_{1-4}$alkyl, aryl, arylC$_{1-4}$alkyl, C$_{3-7}$cycloalkyl, C$_{3-7}$cycloalkylC$_{1-4}$alkyl, Het^1, Het^2, Het^{1}C$_{1-4}$alkyl and Het^{2}C$_{1-4}$alkyl;

whereby R_{11b} may be linked to the remainder of the molecule via a sulfonyl group;

each independently t is zero, 1 or 2;

R_2 is hydrogen or C$_{1-6}$alkyl;

L is -C(=O)-, -O-C(=O)-, -NR$_8$-C(=O)-, -O-C$_{1-6}$alkanediyl-C(=O)-, -NR$_8$-C$_{1-6}$alkanediyl-C(=O)-, -S(=O)$_2$-, -O-S(=O)$_2$-, -NR$_8$-S(=O)$_2$ whereby either the C(=O) group or the S(=O)$_2$ group is attached to the NR$_2$ moiety; and whereby the alkanediyl moiety is optionally substituted with aryl, arylC$_{1-4}$alkyl, C$_{3-7}$cycloalkyl, C$_{3-7}$cycloalkylC$_{1-4}$alkyl, Het^1, Het^2, Het^{1}C$_{1-4}$alkyl and Het^{2}C$_{1-4}$alkyl;

R_3 is C$_{1-6}$alkyl, aryl, C$_{3-7}$cycloalkyl, C$_{3-7}$cycloalkylC$_{1-4}$alkyl, or arylC$_{1-4}$alkyl;

R_4 is hydrogen, C$_{1-4}$alkyloxycarbonyl, carboxyl, aminocarbonyl, mono- or di(C$_{1-4}$alkyl)aminocarbonyl, C$_{3-7}$cycloalkyl, C$_{2-6}$alkenyl, C$_{2-6}$alkynyl or C$_{1-6}$alkyl optionally substituted with aryl, Het^1, Het^2, C$_{3-7}$cycloalkyl, C$_{1-4}$alkyloxycarbonyl, carboxyl, aminocarbonyl, mono- or di(C$_{1-4}$alkyl)aminocarbonyl, aminosulfonyl, C$_{1-4}$alkylS(=O)$_t$, hydroxy, cyano, halogen or amino optionally mono- or disubstituted where the substituents are selected from C$_{1-4}$alkyl, aryl, arylC$_{1-4}$alkyl, C$_{3-7}$cycloalkyl, C$_{3-7}$cycloalkylC$_{1-4}$alkyl, Het^1, Het^2, Het^{1}C$_{1-4}$alkyl and Het^{2}C$_{1-4}$alkyl;

A is C$_{1-6}$alkanediyl, -C(=O)-, -C(=S)-, -S(=O)$_2$-, C$_{1-6}$alkanediyl-C(=O)-, C$_{1-6}$alkanediyl-C(=S)- or C$_{1-6}$alkanediyl-S(=O)$_2$-; whereby the point of attachment to the nitrogen atom is the C$_{1-6}$alkanediyl group in those moieties containing said group;

R_5 is hydrogen, hydroxy, C$_{1-6}$alkyl, Het^{1}C$_{1-6}$alkyl, Het^{2}C$_{1-6}$alkyl, aminoC$_{1-6}$alkyl whereby the amino group may optionally be mono- or di-substituted with C$_{1-4}$alkyl;

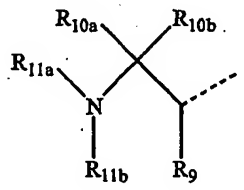
R_6 is C_{1-6}alkyloxy, Het^1, Het^1oxy, Het^2, Het^2oxy, aryl, aryloxy or amino; and in case -A- is other than C_{1-6}alkanediyl then R^6 may also be C_{1-6}alkyl, Het^1C_{1-4}alkyl, Het^1oxyC_{1-4}alkyl, Het^2C_{1-4}alkyl, Het^2oxyC_{1-4}alkyl, arylC_{1-4}alkyl, aryloxyC_{1-4}alkyl or aminoC_{1-4}alkyl; whereby each of the amino groups in the definition of R_6 may optionally be substituted with one or more substituents selected from C_{1-4}alkyl, C_{1-4}alkylcarbonyl, C_{1-4}alkyloxycarbonyl, , aryl, arylcarbonyl, aryloxycarbonyl, Het^1, Het^2, arylC_{1-4}alkyl, Het^1C_{1-4}alkyl or Het^2C_{1-4}alkyl; and

R^5 and $-A-R^6$ taken together with the nitrogen atom to which they are attached may also form Het^1 or Het^2.

2. A compound according to claim 1, wherein

R_1 and R_8 are, each independently, hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, arylC_{1-6}alkyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkylC_{1-6}alkyl, aryl, Het^1, Het^1C_{1-6}alkyl, Het^2, Het^2C_{1-6}alkyl;

R_1 may also be a radical of formula



(II)

wherein

R_9 , R_{10a} and R_{10b} are, each independently, hydrogen, C_{1-4}alkyloxycarbonyl, carboxyl, aminocarbonyl, mono- or di(C_{1-4}alkyl)aminocarbonyl, C_{3-7}cycloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl or C_{1-4}alkyl optionally substituted with aryl, Het^1, Het^2, C_{3-7}cycloalkyl, C_{1-4}alkyloxycarbonyl, carboxyl, aminocarbonyl, mono- or di(C_{1-4}alkyl)aminocarbonyl, aminosulfonyl, C_{1-4}alkyl$S(O)_t$, hydroxy, cyano, halogen or amino optionally mono- or disubstituted where the substituents are selected from C_{1-4}alkyl, aryl, arylC_{1-4}alkyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkylC_{1-4}alkyl, Het^1, Het^2, Het^1C_{1-4}alkyl and Het^2C_{1-4}alkyl; whereby R_9, R_{10a} and the carbon atoms to which they are attached may also form a C_{3-7}cycloalkyl radical;

R_{11a} is hydrogen, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-7}cycloalkyl, aryl, aminocarbonyl optionally mono- or disubstituted, aminoC_{1-4}alkylcarbonyloxy optionally mono- or disubstituted, C_{1-4}alkyloxycarbonyl, aryloxycarbonyl, Het^1oxycarbonyl, Het^2oxycarbonyl, aryloxycarbonylC_{1-4}alkyl, arylC_{1-4}alkyloxycarbonyl, C_{1-4}alkylcarbonyl, C_{3-7}cycloalkylcarbonyl, C_{3-7}cycloalkylC_{1-4}alkyloxycarbonyl, C_{3-7}cycloalkylcarbonyloxy, carboxylC_{1-4}alkylcarbonyloxy, C_{1-4}alkylcarbonyloxy, arylC_{1-4}alkyl-

carbonyloxy, arylcarbonyloxy, aryloxycarbonyloxy, Het^1carbonyl, Het^1carbonyloxy, Het^1C_{1-4}alkyloxycarbonyl, Het^2carbonyloxy, Het^2C_{1-4}alkylcarbonyloxy, Het^2C_{1-4}alkyloxycarbonyloxy or C_{1-4}alkyl optionally substituted with aryl, aryloxy, Het^2 or hydroxy; wherein the substituents on the amino groups are each independently selected from C_{1-4}alkyl, aryl, arylC_{1-4}alkyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkylC_{1-4}alkyl, Het^1, Het^2, Het^1C_{1-4}alkyl and Het^2C_{1-4}alkyl;

R_{11b} is hydrogen, C_{3-7}cycloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, aryl, Het^1, Het^2 or C_{1-4}alkyl optionally substituted with halogen, hydroxy, C_{1-4}alkylS(=O)$_t$, aryl, C_{3-7}cycloalkyl, Het^1, Het^2, amino optionally mono- or disubstituted where the substituents are selected from C_{1-4}alkyl, aryl, arylC_{1-4}alkyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkylC_{1-4}alkyl, Het^1, Het^2, Het^1C_{1-4}alkyl and Het^2C_{1-4}alkyl;

whereby R_{11b} may be linked to the remainder of the molecule via a sulfonyl group;

each independently t is zero, 1 or 2;

R_2 is hydrogen or C_{1-6}alkyl;

L is -C(=O)-, -O-C(=O)-, -NR_8-C(=O)-, -O–C_{1-6}alkanediyl-C(=O)-, -NR_8–C_{1-6}alkanediyl-C(=O)-, -S(=O)$_2$-, -O-S(=O)$_2$-, -NR_8-S(=O)$_2$ whereby either the C(=O) group or the S(=O)$_2$ group is attached to the NR_2 moiety;

R_3 is C_{1-6}alkyl, aryl, C_{3-7}cycloalkyl, C_{3-7}cycloalkylC_{1-4}alkyl, or arylC_{1-4}alkyl;

R_4 is hydrogen, C_{1-4}alkyloxycarbonyl, carboxyl, aminocarbonyl, mono- or di(C_{1-4}alkyl)aminocarbonyl, C_{3-7}cycloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl or C_{1-6}alkyl optionally substituted with aryl, Het^1, Het^2, C_{3-7}cycloalkyl, C_{1-4}alkyloxycarbonyl, carboxyl, aminocarbonyl, mono- or di(C_{1-4}alkyl)aminocarbonyl, aminosulfonyl, C_{1-4}alkylS(=O)$_t$, hydroxy, cyano, halogen or amino optionally mono- or disubstituted where the substituents are selected from C_{1-4}alkyl, aryl, arylC_{1-4}alkyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkylC_{1-4}alkyl, Het^1, Het^2, Het^1C_{1-4}alkyl and Het^2C_{1-4}alkyl;

A is C_{1-6}alkanediyl, -C(=O)-, -C(=S)-, -S(=O)$_2$-, C_{1-6}alkanediyl-C(=O)-, C_{1-6}alkanediyl-C(=S)- or C_{1-6}alkanediyl-S(=O)$_2$-; whereby the point of attachment to the nitrogen atom is the C_{1-6}alkanediyl group in those moieties containing said group;

R_5 is hydrogen, hydroxy, C_{1-6}alkyl, Het^1C_{1-6}alkyl, Het^2C_{1-6}alkyl, aminoC_{1-6}alkyl whereby the amino group may optionally be mono- or di-substituted with C_{1-4}alkyl;

R_6 is C_{1-6}alkyloxy, Het^1, Het^1oxy, Het^2, Het^2oxy, aryl, aryloxy or amino; and in case -A- is other than C_{1-6}alkanediyl then R^6 may also be C_{1-6}alkyl, Het^1C_{1-4}alkyl,

$Het^1oxyC_{1-4}alkyl$, $Het^2C_{1-4}alkyl$, $Het^2oxyC_{1-4}alkyl$, $arylC_{1-4}alkyl$, $aryloxyC_{1-4}alkyl$ or $aminoC_{1-4}alkyl$; whereby each of the amino groups in the definition of R_6 may optionally be substituted with one or more substituents selected from $C_{1-4}alkyl$, $C_{1-4}alkylcarbonyl$, $C_{1-4}alkyloxycarbonyl$, aryl, arylcarbonyl, aryloxycarbonyl, Het^1, Het^2, $arylC_{1-4}alkyl$, $Het^1C_{1-4}alkyl$ or $Het^2C_{1-4}alkyl$; and

R^5 and $-A-R^6$ taken together with the nitrogen atom to which they are attached may also form Het^1 or Het^2.

3. A compound according to any of claims 1 or 2 wherein R_1 hydrogen, $C_{1-6}alkyl$, $C_{2-6}alkenyl$, $arylC_{1-6}alkyl$, $C_{3-7}cycloalkyl$, $C_{3-7}cycloalkylC_{1-6}alkyl$, aryl, Het^1, $Het^1C_{1-6}alkyl$, Het^2, $Het^2C_{1-6}alkyl$; wherein Het^1 is a saturated or partially unsaturated monocyclic heterocycle having 5 or 6 ring members, which contains one or more heteroatom ring members selected from nitrogen, oxygen or sulfur and which is optionally substituted on one or more carbon atoms.

4. A compound according to any of claims 1 to 3 wherein L is $-O-C_{1-6}alkanediyl-C(=O)-$.

5. A compound according to any one of claims 1 to 3 wherein L is $-O-C(=O)-$.

6. A compound according to any one of claims 1 to 3 wherein L is $-NR_8-C_{1-6}alkanediyl-C(=O)-$, whereby the alkanediyl moiety is optionally substituted with, aryl, $arylC_{1-4}alkyl$, Het^1, Het^2, $Het^1C_{1-4}alkyl$ and $Het^2C_{1-4}alkyl$.

7. A compound according to any one of claims 1 to 6 wherein R_1 is Het^1, $Het^1C_{1-6}alkyl$, Het^2 or $Het^2C_{1-6}alkyl$.

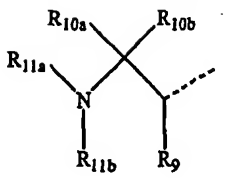
8. A compound according to claim 7 wherein R_1 is Het^1 or Het^2.

9. A compound according to claim 8 wherein R_1 is Het^1.

10. A compound according to claim 9 wherein R_1 is hexahydro-furo[2,3-b]-furanyl.

11. A compound according to claim 10 wherein R_1 is tetrahydrofuranyl.

12. A compound according to any one of claims 1 to 6 wherein L is $-O-C_{1-6}alkanediyl-C(=O)-$ or $-NR_8-C_{1-6}alkanediyl-C(=O)-$ and R_1 is a radical of formula



(II)

wherein

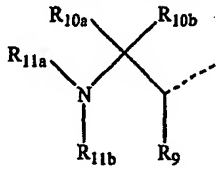
R_9 is oxo ,

R_{10a} and R_{10b} are, each independently, hydrogen or C_{1-4}alkyl optionally substituted with aryl, Het^1, Het^2, C_{1-4}alkyloxycarbonyl, carboxyl, aminocarbonyl, hydroxy, or amino optionally mono- or disubstituted where the substituents are selected from C_{1-4}alkyl,

R_{11a} is arylC_{1-4}alkyl, or C_{1-4}alkyl optionally substituted with aryl or halogen and

R_{11b} is hydrogen, or C_{1-6}alkyloxycarbonyl.

13. A compound according to claim 12 wherein L is -O-C_{1-6}alkanediyl-C(=O)- or -NR_8-C_{1-6}alkanediyl-C(=O)- and R_1 is a radical of formula



(II)

wherein

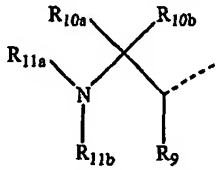
R_9 is oxo ,

R_{10a} and R_{10b} are hydrogen,

R_{11a} is arylC_{1-4}alkyl wherein the aryl group is substituted with a halogen and

R_{11b} is hydrogen, or C_{1-6}alkyloxycarbonyl.

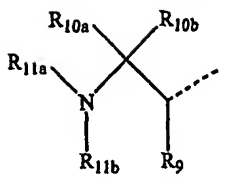
14. A compound according to claim 13 wherein L is -O-C_{1-6}alkanediyl-C(=O)- or -NR_8-C_{1-6}alkanediyl-C(=O)- and R_1 is a radical of formula



(II)

wherein R_9 is oxo , R_{10a} and R_{10b} are hydrogen, R_{11a} is *m*-fluorobenzyl and R_{11b} is hydrogen, or C_{1-6}alkyloxycarbonyl.

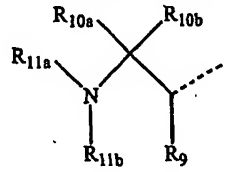
15. A compound according to claim 14 wherein L is -O-C_{1-6}alkanediyl-C(=O)- or -NR_8-C_{1-6}alkanediyl-C(=O)- and R_1 is a radical of formula



(II)

wherein R_9 is oxo, R_{10a} and R_{10b} are hydrogen, R_{11a} is *m*-fluorobenzyl and R_{11b} is hydrogen.

16. A compound according to claim 14 wherein L is -O-C_{1-6}alkanediyl-C(=O)- or -NR_8-C_{1-6}alkanediyl-C(=O)- and R_1 is a radical of formula



(II)

wherein R_9 is oxo, R_{10a} and R_{10b} are hydrogen, R_{11a} is *m*-fluorobenzyl and R_{11b} is tert-butyloxycarbonyl.

17. A compound according to any one of claims 1 to 16 wherein R_3 is arylC_{1-4}alkyl.

18. A compound according to claim 17 wherein R_3 is arylCH_2-.

19. A compound according to claim 18 wherein R_3 is benzyl.

20. A compound according to any one of claims 1 to 19 wherein R_4 is C_{1-6}alkyl.

21. A compound according to claim 20 wherein R_4 is butyl.

23. A compound according to claim 21 wherein R_4 is isobutyl.

23. A compound according to any one of claims 1 to 22 wherein

A is C_{1-6}alkanediyl, -C(=O)- or C_{1-6}alkanediyl-C(=O)-; whereby the point of attachment to the nitrogen atom is the C_{1-6}alkanediyl group in those moieties containing said group;

R_5 is hydrogen, C_{1-6}alkyl, Het^1C_{1-6}alkyl, Het^2C_{1-6}alkyl, aminoC_{1-6}alkyl whereby the amino group may optionally be mono- or di-substituted with C_{1-4}alkyl; and

in case –A- is –C(=O)- then R^6 is C_{1-6}alkyloxy, Het^1, Het^1oxy or Het^2oxy, aryl, Het^1C_{1-4}alkyl, Het^1oxyC_{1-4}alkyl, Het^2C_{1-4}alkyl, Het^2oxyC_{1-4}alkyl, arylC_{1-4}alkyl, aryloxyC_{1-4}alkyl or aminoC_{1-4}alkyl; and

in case –A- is C_{1-6}alkanediyl then R^6 is amino, C_{1-6}alkyloxy, Het^1, Het^1oxy or Het^2oxy; and

in case –A- is C_{1-6}alkanediyl-C(=O)- then R^6 is C_{1-6}alkyloxy, Het^1, Het^1oxy or Het^2oxy, aryl, C_{1-6}alkyl, Het^1C_{1-4}alkyl, Het^1oxyC_{1-4}alkyl, Het^2C_{1-4}alkyl, Het^2oxyC_{1-4}alkyl, $arylC_{1-4}$alkyl, $aryloxyC_{1-4}$alkyl or $aminoC_{1-4}$alkyl;

whereby each of the amino groups in the definition of R_6 may optionally be substituted with one or more substituents selected from C_{1-4}alkyl, C_{1-4}alkylcarbonyl, C_{1-4}alkyloxycarbonyl, aryl, arylcarbonyl, aryloxycarbonyl, Het^1, Het^2, $arylC_{1-4}$alkyl, Het^1C_{1-4}alkyl or Het^2C_{1-4}alkyl; and

R^5 and –A-R^6 taken together with the nitrogen atom to which they are attached may also form Het^1 whereby Het^1 is substituted by at least an oxo group.

24. A compound according to claim 23 wherein R_5 is hydrogen or C_{1-6}alkyl.

25. A compound according to claim 24 wherein R_5 is hydrogen.

26 A compound according to claim 24 wherein R_5 is methyl or ethyl.

27. A compound according to claim 26 wherein R_5 is methyl.

28. A compound according to claim 23 wherein A is C_{1-6}alkanediyl.

29. A compound according to claim 28 wherein A is ethylenediyl.

30. A compound according to any one of claims 1 to 29 wherein R_6 is a Het^1.

31. A compound according to claim 30 wherein R_6 is a Het^1C_{1-4}alkyl.

32. A compound according to claim 30 wherein R_6 is a pyrrolidinyl or $pyrrolidinylC_{1-4}$alkyl.

33. A compound according to claim 32 wherein R_6 is a pyrrolidinylethyl.

34. A compound according to any one of claims 1 to 29 wherein R_6 is an amino; whereby each of the amino groups may optionally be substituted with one or more substituents selected from C_{1-4}alkyl, C_{1-4}alkylcarbonyl, C_{1-4}alkyloxycarbonyl, aryl, arylcarbonyl, aryloxycarbonyl, Het^1, Het^2, $arylC_{1-4}$alkyl, Het^1C_{1-4}alkyl or Het^2C_{1-4}alkyl.

35. A compound according to claim 34 wherein R_6 is an amino; whereby each of the amino group is substituted with two substituents selected from C_{1-4}alkyl.

36. A compound according to claim 35 wherein R_6 is dimethylamino.

37. A compound according to claim 1 having the formula

(1-Benzyl-3-{[2-(2-dimethylamino-ethylamino)-benzothiazole-6-sulfonyl]-isobutyl-amino}-2-hydroxy-propyl)-carbamic acid hexahydro-furo[2,3-b] furan-3-yl ester,

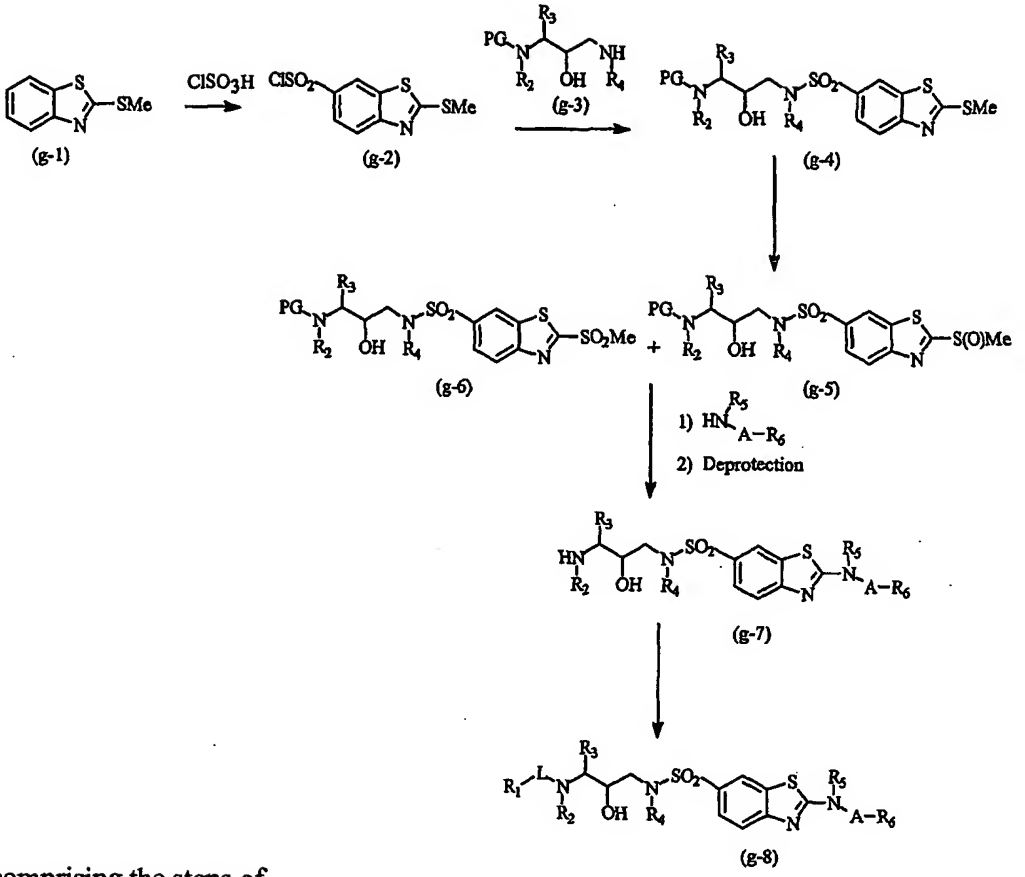
(1-Benzyl-3-{[2-(2-dimethylamino-ethylamino)-benzothiazole-6-sulfonyl]-isobutyl-amino}-2-hydroxy-propyl)-carbamic acid tetrahydro-furan-3-yl ester,

1-Benzyl-2-hydroxy-3-{isobutyl-[2-(2-pyrrolidin-1-yl-ethylamino)-benzothiazole-6-sulfonyl]-amino}-propyl)-carbamic acid hexahydro-furo[2,3-b] furan-3-yl ester,

[1-Benzyl-3-({2-[(3-dimethylamino-propyl)-methyl-amino]-benzothiazole-6-sulfonyl}-isobutyl-amino)-2-hydroxy-propyl]-carbamic acid hexahydro-furo[2,3-b] furan-3-yl ester,

[1-Benzyl-3-({2-[(1-ethyl-pyrrolidin-2-ylmethyl)-amino]-benzothiazole-6-sulfonyl}-isobutyl-amino)-2-hydroxy-propyl]-carbamic acid hexahydro-furo[2,3-b] furan-3-yl ester.

38. Method for the preparation of a compound according to claim 1 according to the scheme G



comprising the steps of

a) reacting benzothiazole derivative **g-1** with chlorosulfonic acid, and subsequently with thionylchloride to yield intermediate **g-2**,

b) reacting said intermediate **g-2** with intermediate **g-3** yielding an intermediate **g-4** wherein PG is a protecting group,

c) reacting intermediate **g-4** into intermediates **g-5** and **g-6**,

d) intermediates **g-5** and **g-6** are derivatized with a compound of formula $HN(R_5)A\text{-}R_6$ yielding and subsequently deprotected yielding intermediate **g-7**,

e) **g-7** may then be reacted with an intermediate of formula $R_1\text{-}L\text{-}$(leaving group) resulting in the compound **g-8**.

39. A method according to claim 38 wherein the protecting group is Boc.

40. A method according to any one of claims 38 or 39 wherein step (c) is performed with a suitable reagent selected from the group comprising meta-chloroperoxybenzoic acid or magnesium monoperoxyphtalate hexahydrate.

41. A pharmaceutical composition, comprising an effective amount of at least one compound as claimed in any one of claims 1 to 37, and a pharmaceutically tolerable excipient.

42. A method of inhibiting a protease of a multi-drug resistant retrovirus in a mammal infected with said retrovirus, comprising administering a protease inhibiting amount of a compound according to any one of claims 1 to 37 to said mammal in need thereof.

43. A method of treating or combating infection or disease associated with multi-drug resistant retrovirus infection in a mammal, comprising administering an effective amount of at least one compound according to any one of claims 1 to 37 to said mammal.

44. A method of inhibiting multi-drug resistant retroviral replication, comprising contacting a retrovirus with an effective amount of at least one compound according to any one of claims 1 to 37.

45. The method as claimed in claim 42, 43 or 44 wherein the retrovirus is a human immunodeficiency virus (HIV).

46. A compound as claimed in any one of claims 1 to 37 for use as a medicine.

47. The use of a compound as claimed in any one of claims 1 to 37 in the manufacture of a medicament for treating or combating infection or disease associated with multi-drug resistant retrovirus infection in a mammal.

48. The use of a compound as claimed in any one of claims 1 to 37 in the manufacture of a medicament for inhibiting a protease of a multi-drug resistant retrovirus in a mammal infected with said retrovirus.

49. The use of a compound as claimed in any one of claims 1 to 37 in the manufacture of a medicament for inhibiting multi-drug resistant retroviral replication.

50. The use according to any one of claims 47 to 49 wherein the retrovirus is a human immunodeficiency virus (HIV).

51. A compound according to claim 1 wherein the compound is listed in table 8.

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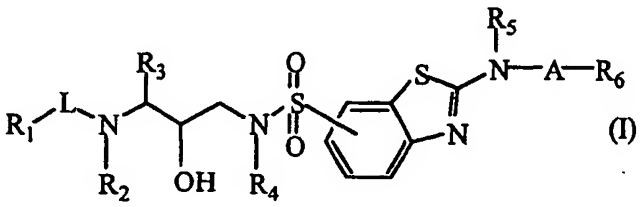
(54) Title: BROADSPECTRUM 2-(SUBSTITUTED-AMINO)-BENZOTHIAZOLE SULFONAMIDE HIV PROTEASE INHIBITORS



(I)

(57) Abstract: The present invention concerns the compounds having the formula (I), N-oxides, salts, stereoisomeric forms, racemic mixtures, prodrugs, esters and metabolites thereof, wherein R_1 and R_8 each are H, optionally substituted C_{1-6}alkyl, C_{2-6}alkenyl, C_{3-7}cycloalkyl, aryl, Het^1, Het^2; R_1 may also be a radical of formula $(R_{11a}R_{11b})NC(R_{10a}R_{10b})CR_{9-}$; t is 0, 1 or 2; R_2 is H or C_{1-6}alkyl; L is -C(=O)-, -O-C(=O)-, -NR_8-C(=O)-, -O-C_{1-6}alkanediyl-C(=O)-, -NR_8-C_{1-6}?alkanediyl-C(=O)-, -S(=O)2-, -O-S(=O)$_{2-}$, -NR8-S(=O)$_2$; R3 is C_{1-6}alkyl, aryl, C_{3-7}cycloalkyl, C_{3-7}cycloalkylC_{1-4}alkyl, or arylC_{1-4}alkyl; R_4 is H, C_{1-4}alkylOC(=O), carboxyl, aminoC(=O), mono- or di(C_{1-4}alkyl)aminoC(=O), C_{3-7}cycloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl or optionally substituted C_{1-6}alkyl; A is C_{1-6}alkanediyl, -C(=O)-, -C(=S)-, -S(=O)$_{2-}$, C_{1-6}alkanediyl-C(=O)-, C_{1-6}alkanediyl-C(=S)- or C_{1-6}alkanediyl-S(=O)$_{2-}$; R_5 is H, OH, C_{1-6}alkyl, Het^1C_{1-6}alkyl, Het^2C_{1-6}alkyl, optionally substituted aminoC_{1-6}alkyl; R_6 is C_{1-6}alkylO, Het^1, Het^{1O}, Het^2, Het^2O, aryl, arylO, C_{1-6}alkyloxycarbonylamino or amino; and in case -A- is other than C_{1-6}alkanediyl then R^6 may also be C_{1-6}alkyl, Het^1C_{1-4}alkyl, Het^1OC_{1-4}alkyl, Het^2C_{1-4}alkyl, Het^2OC_{1-4}alkyl, arylC_{1-4}alkyl, arylOC_{1-4}alkyl or aminoC_{1-4}alkyl; whereby each of the amino groups in the definition of R^6 may optionally be substituted; R^5 and -A-R^6 taken together with the nitrogen atom to which they are attached may also form Het^1 or Het^2. It further relates to their use as broadspectrum HIV protease inhibitors, processes for their preparation as well as pharmaceutical compositions and diagnostic kits comprising them. It also concerns combinations thereof with another anti-retroviral agent, and to their use in assays as reference compounds or as reagents.

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International Application No
PCT/EP 02/01788

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D277/82 A61K31/428 C07D493/04 C07D401/12 C07D417/12 A61P31/18

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 99 65870 A (FURFINE ERIC STEVEN ;SPALTENSTEIN ANDREW (US); VERTEX PHARMA (US);) 23 December 1999 (1999-12-23) example 114	1-51
Y	WO 96 28463 A (DEVADAS BALEKUDRU ;MCDONALD JOSEPH J (US); VAZQUEZ MICHAEL L (US);) 19 September 1996 (1996-09-19) cited in the application * see pp 159-164, 175-177 *	1-51
Y	WO 95 06030 A (MUELLER RICHARD A ;VAZQUEZ MICHAEL L (US); MONSANTO CO (US); SEARL) 2 March 1995 (1995-03-02) cited in the application page 194-195; examples 19D,18F	1-51

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
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Name and mailing address of the ISA	Authorized officer
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